Esophageal and Gastric Disorders in Infancy and Childhood

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Editors

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To my three marvelous girls Ella, Jess, and Flo for teaching me the importance of life outside work, to my wonderful wife Kay for being my best friend, and to my Dad for inspiring me to follow the medical path.

Mike Thomson

To what's truly important in life, my family especially the boys Karl and Dan, and my coeditors especially JEF, it has been a pleasure to work with you all.

Khalid M. Khan

To my family, who supported me all these years and taught me never to give up. It was worth it!

Holger Till

Preface

This book owes its existence to the families who brought us their babies with the difficult problem of esophageal atresia. Other families have similarly inspired each of the editors and authors of this book in their continuing efforts to treat the many difficult esophageal and gastric disorders which occur in childhood. We acknowledge our feelings of great indebtedness to these patients and families. They offered us the privilege to learn from them.

Originally, the book was only going to be a how-to-do-it surgery book, but it rapidly grew into a multidisciplinary effort. We quickly realized we needed to enlist a number of distinguished pediatric gastroenterologists as well as other pediatric surgeons to provide the necessary information. As the result of everyone's efforts, this book offers a comprehensive and detailed approach to these complex patients. We believe this is an informative and detailed resource which will be of great value for all workers in this field, but we look forward to your judgment.

Of course, the success of this book is dependent on each author's contribution, and we cannot thank them enough for their scholarly chapters and their patience. Moreover, each editor dedicated a great deal of time and energy to review the proofs. Finally, Holger and Mike, sharing the leading editorship equally, created the connections among the articles and shaped it into a unified piece of work. Of course many other peopled supported this process tremendously like Sandra Becker, Mary Merrit and Bharatwaj M.V. We thank you all.

Last but not least we return the love and energy of our families, who shared our enthusiasm and gave us strength to accomplish this work.

On behalf of all authors, editors, families, and friends, we dedicate this book to our patients and the future challenges this field presents.

Yours sincerely,
The Editors

Postscript:
Mike Thomson would like to acknowledge his coeditors in their unstinting energy and application toward the eventual conclusion of this book. He would also like to pay tribute to the patience and understanding of his friends as authors who have contributed to this massive piece of work, without whom this would not have been even remotely a feasible venture. Thank you so much for your patience while this long gestation came about. Lastly he would

like to thank most deeply for their support and, at times, bewildering faith in this project his family – Kay, his lovely friend and wife and partner, Ella, Jess, and Flo, his wildly amazing and fast-growing up daughters.

Introduction

The outlook for pediatric patients should be for 70 or more good years, a timeline which leaps well past the traditional therapeutic mileposts of length of stay (LOS) and even 5- and 10-year outcomes. The subject of this book, *Esophageal and Gastric Disorders of Infancy and Childhood*, includes some of the most serious birth defects as well as such common but potentially severe problems as gastroesophageal reflux (GER). As will be emphasized, these lesions and disorders may also have significant later consequences, and therefore success beyond childhood will likely depend on the effectiveness and durability of the early treatment. Clearly, the specific problems, if not well managed, will stand in the way of realizing 70 or more good years. Although this long-term goal may be difficult to achieve, the recent and continuing advances described in these chapters now make it increasingly possible.

The editors have designed this book *Esophageal and Gastric Disorders in Infants and Children* to be of value to all workers in this area, even the most experienced and knowledgeable. To be sure, this is also a lofty goal, and to accomplish it we have included a wide range of features in this book to broaden its value. First, both medical and surgical chapters are included and equally emphasized. Certainly, more and more information is becoming available in both the medical and surgical fields making it difficult to keep up in one's own specialty much less in other areas. The selection of the best treatment plan, however, requires some understanding of the benefits and consequences of the various options even though they may be outside of one's specialty.

Our experience has also indicated that there is less and less shared understanding between pediatricians and surgeons despite protestations from the "best" centers that this is "not true at our place." Either medical or surgical therapy will likely have benefits, especially initially, but limitations may appear over the long term, increasing the importance of the treatment decision. This book will provide the practitioner with the information on which to base these decisions. The organization of the major sections begins with normal development and function, followed by the biological bases of the disease problems to provide a background for reviewing the benefits and consequences of the therapeutic approaches. The biological features are emphasized throughout the book which we believe will make it easier to interpret the clinical situations encountered.

This book initially was to be limited to pediatric esophageal problems. As we began working with the esophageal topics, however, the stomach kept

intruding whether through the gastroesophageal junction or into the chest itself. Function moves downward while damage usually flows upward. The esophageal and gastric mucosal layers were active, intertwined, could undergo a variety of unsatisfactory changes with inflammation and injury, and were difficult to separate. Clearly, these two organs seemed to belong together from both medical and surgical standpoints.

With the scope of the book determined, the topics were selected to cover the significant biological, medical, and surgical issues of the pediatric esophagus and stomach. The distinguished contributing authors have been chosen for their insight into these problems and treatments. The range and depth provided will not only provide comprehensive current information but also establish a framework on which to build. Knowledge will continue to move ahead and a solid conceptual background will be valuable to adding and understanding future advances.

An insightful presentation of the diseases and treatments is also of real value because a worldwide consensus and uniform approach to these problems often does not currently exist. Despite the efforts of many workers in the field and attempts to provide well-reasoned recommendations, little seems to be settled in the minds of practitioners. Even for common problems such as GER and esophageal strictures, we have found individual conclusions about the severity of the findings and the resulting treatment plans not only vary widely across the world but even within institutions. The assessment and treatment of reflux, for example, is surprisingly varied among pediatricians and surgeons, and not just between them. This is despite the efforts of acknowledged experts to set detailed guidelines. For GER, the methods and difficulties of diagnosis and the judgment of its significance, as well as the evaluation of potential treatments, all pose difficulties. This book, by fully presenting the issues, should improve understanding and lead to more effective therapy.

The goal of 70 years or more also requires the active pursuit of normality. To reach this goal follow-up evaluations and treatments should be continued as necessary to be sure normality remains in sight. What will be needed in follow-up will often depend on an understanding of the longer term effects of both the abnormalities and the treatments, and this may be provided by well-designed prospective studies. At present, while evidence-based decision-making is certainly a worthwhile goal, it is in limited supply. We anticipate that the authors of this book will continue to be leaders in developing well-designed studies. However, in the meantime, practitioners must select and provide treatment based on the information available. The contents of this book will be aimed to aid the practitioner in making these decisions.

The biological underpinning of the clinical situations is of particular importance for pediatric problems. Not only are most congenital defects the result of developmental abnormalities, but there is also an active background of continuing normal development, which increases complexity in management generally. What might seem to be routine treatments with defined consequences in the adult population may be of far greater significance in the infant and child. Of course, there are significant biological factors in the treatment of adult patients but active development has ended, leaving the background reasonably stable.

In children, therapy directed at a disease process will be superimposed on continuing normal development and all are inter-related and may be affected. Whether medical or surgical, any therapy which affects function or anatomy over a long period will likely have several consequences. The commonly used acid suppression treatment of reflux esophagitis, for example, may produce significant effects on the development of the stomach, in particular, the acid-producing cells. Other areas of development may also be affected by the medications and, perhaps, impaired calcification will lead to decreased bone density. Such considerations become greater the longer the planned therapy.

Common surgical operations, such as fundoplication, may also have significant later consequences. A thoracotomy incision which results in the fusion of ribs and/or the loss of innervation of the serratus anterior muscle might produce significant problems including scoliosis. Granted, no current operation is in its final form, but the principles and details that comprise the surgical goals should be accessible and are some of the additional considerations that must be factored in when selecting therapy. Consequently, each surgical writer will present not only the indications for the operations along with the important details that will make for a successful repair but also, as far as possible, the long-term biological consequences and later problems associated with them. These issues are present in virtually all therapeutic choices and have increased importance when carried out against the background of growth and development. Predictably, the longer view will be more and more thrust upon us.

In keeping with the long view in treating these patients, it is recognized that many of these esophageal and gastric disorders may have significant later consequences. Another feature of this book, therefore, has been carrying the information on the disease processes and effects of treatment into early adulthood. For those caring for children, there almost seems to be an assumption that life does not go much beyond age 16, a proposition for which there is little evidence. The teenager is handed off "doing well" to practitioners caring for young adults and, in effect, disappears. The later consequences, however, of GER and the long-term effects of the other types of treatment used in childhood, whether medical or surgical, illustrate the importance of the longer view.

Treatment may require a choice between a relatively easy short-term solution and one that appears more difficult but which has significant long-term advantages. This conflict is most often present in surgical approaches. An operation which produces a desirable short LOS does not necessarily place the child on a path to 70 or more good years. This goal may be an unwelcome burden for the surgeon whose peace of mind as well as reputation depends on a shorter LOS and the occurrence of only "acceptable" complications. Problems which may occur 20 or 30 years later may not even be considered. The spread of information and the inevitable increasing emphasis on long-term results, however, will make these considerations necessary.

The therapy of difficult lesions and diseases may run the risk of setting in motion new problems or the substitution of one disease state for another. Palliative solutions are sometimes necessary but, by definition, bring their own form of chronic problems, and, with time, the deficiencies will become

increasingly apparent. Transplantation, with the need to hold off rejection, provides a clear example of the problems that predictably result from substituting one disease for another. Less obvious are other treatments which significantly alter anatomy and function, such as interposition grafts for esophageal atresia (EA), but the consequences may also be unsatisfactory. Palliation, although accepted and sometimes necessary, should be limited for the best long-term results.

We have emphasized the biological theme of this book, as is well illustrated by the chapters on the recent enlistment of developmental responses to solve some of the most severe problems. The use of growth induction on the small esophageal segments for patients with esophageal atresia (EA), for example, provides a biological solution for the traditionally difficult defect of long-gap esophageal atresia (LG-EA). At the extreme end of the EA spectrum, the entire thoracic esophagus may be missing, making the possibility of using only the esophagus for the repair apparently impossible. The developmental potential, however, is great and even very small (2–3 mm) esophageal primordia have been induced to grow into an outwardly normal lower esophagus. This has been a spectacular example of using a biology-based therapy to solve the problem of a significant congenital defect (Chaps. 22 and 25). Long, recalcitrant esophageal strictures have also been difficult to treat and typically have led to gastric or colon interpositions. A variation on the tension-induced esophageal growth approach has been used to treat the significant problem of long strictures by using staged resections with greatly improved long-term results (Chapter 34). These are the most noteworthy examples of the biological approach but others will follow.

Another strength of this book is the detailed explanations of the surgical treatment of some of the most severe problems. Growth induction provides an excellent solution to LG-EA, but less well known are the technical difficulties in achieving a good growth response. The details helpful in growth induction as well as in the surgical treatment of related problems such as the difficult esophageal anastomosis, tracheomalacia, and re-operative strategies among other procedures are presented. These descriptions will overcome the space and page limitations of journal articles and be valuable to surgeons.

A developmental solution requires that the defect is not primarily genetic in origin and all the information necessary for a catch-up response is present. Although congenital defects are often loosely thought to be genetic in origin, the evidence suggests these problems arise primarily from faulty development. EA, for example, seems to result from the faulty budding of the trachea from the primordial esophageal tube and the creation of a gap between the upper and lower esophageal segments. With the segments separated and the entire esophagus no longer acted on by the tension of the growing spinal column, the gap may increase in length. The outwardly wide EA spectrum predictably begins with a central defect and is determined by the length of the gap and the presence or absence of residual fistulas into the airway.

Despite the apparent complexity of the EA spectrum, development can be effectively restarted. Only the signal is missing which is able to trigger the well-orchestrated three-dimensional growth seen during development. Catch-up growth can be reliably induced in the small and widely separated

esophageal segments by providing the missing signal. The signals themselves have usually proven to be very straightforward biomechanical stimuli, and for the esophagus, axial tension will produce effective growth of the smallest segments. The tension principle of esophageal growth induction, as noted, has also been extended to acquired problems, such as long recalcitrant strictures.

When a principle is basic and effective, it is likely to have other general applications with improved treatment solutions. Although not applicable to every problem, there are other examples of tissue or organ deficiency where it has been used with impressive results. For patients with a hypoplastic cardiac ventricle, induced growth has produced two usable ventricles and has avoided a palliative solution which brings increasing problems over the succeeding years. Currently, an intra-abdominal testis is most commonly treated by dividing the arterial blood supply, losing most, if not all, function. Traction, however, will stimulate catch-up length and an improved result. Deficiencies of skin and abdominal wall are commonly treated with tissue expanders to aid closure. These devices were initially thought to involve only skin stretching, but basic studies have shown a proliferative response to the tension by the many cell types involved. Effective induced lengthening of the remaining intestine in the short gut syndrome would greatly speed the transition from hyper-alimentation and costly elemental solutions to a more normal diet. For all of these problems, as with LG-EA, the traditional treatments have been palliative or otherwise unsatisfactory for the long term. The use of these biological solutions with the induction of normal development has moved the outlook for these patients far closer to normal, with fewer adverse consequences and better long-term results.

When we focus on anatomy, embryology, and function dependent on these abnormalities which are caused by chance, we must remember that medicine has evolved massively over the last 30 years and that approaches which are not just reparative in a surgical sense may be beneficial to the quality of life of an individual affected by such issues. Indeed the advances in medical and pharmaceutical approaches have been enormous in this time span and should be and are, emphasized, within this text. For instance, it was only understood in the early 1990s that *Helicobacter pylori* was the primary cause of peptic ulcer disease and not, as previously thought, an overactive vagal nerve stimulated acid production from the stomach. So went Billroth-type operations and selective vagotomies. Medical approaches recently have therefore challenged surgery to produce reasons for the traditional approaches, and we see the obvious advantages now. Similarly, surgical solutions such as open fundoplication have been supplanted by laparoscopic approaches which, in turn, have been challenged by endoscopic trans-oral approaches – which are receiving a great deal of attention at present and are promising. Long-term anti-acid medical treatments are generally safe and may be attached to less morbidity than surgical solutions, and this area has received considerable attention in this book. So, while medical and surgical approaches are both effective, it must be identified that a joint approach in pediatrics is mandatory if we are to achieve a balanced management strategy for many of these complex conditions. We would never suggest that a pure surgical or medical approach is ideal for an

empyema or a subdural hematoma, for example, and this is equally true in this field involving the upper GI tract. This is what makes this book unique – as, for the first time, surgeons and pediatric gastroenterologists have come together to produce the first text on these complex topics which is of a bilateral genre. Pediatric gastroenterologists and surgeons alike do not live and work in bubbles isolated from one another in the real world but work in superb harmony (in the best centers) and to the advantage of the families and children they serve. Long may this continue and we hope that this text will serve to perfect that partnership as the editorship has also done. When we look to the future, we can see many options and opportunities that involve closer collaboration between medical and surgical GI doctors and teams. They may also involve such specialities as bioengineering, molecular biology, genetics, neuroimmunology, neurogenetics, tissue modeling, etc., but not forgetting the traditional team-orientated approaches involving our colleagues in GI physiology, feeding therapy, psychology, dietetics, GI nursing, stoma therapy, and pharmacology to name only a few. We hope that this multispecialty book will appeal and educate many within our multidisciplinary specialty and conjoin medicine and surgery toward a greater theme which is collaboration and a more effective collateral approach going forward.

As stated at the beginning of the Introduction, the goal in pediatric therapy must be for 70 or more good years, and this is a stringent requirement. The problems encountered in pediatric patients are a unique mixture of developmental and genetic defects, which play out on a continuing background of normal and abnormal development. For these young patients, the often long-range consequences of both diseases and treatments must also be kept in mind. The aim of this book is to clarify as much as possible these complex events and the therapeutic options. Treatments which enlist normal biological responses, we believe, will have particular value and, as this approach becomes better understood and the applications expand in number, the goal of 70 or more good years will come into view for even the most difficult of these problems.

Contents

Part I

Introduction

The Biology of Defects, Disease, and Treatments

1

John E. Foker

The origins of this book began with the success in growing the smallest esophageal segments to normal size in patients with esophageal atresia (EA). It had become clear that the growth procedure effectively tapped into the considerable developmental potential of even the most rudimentary blind ends of the esophagus allowing the benefits of a true primary repair to be realized across the full EA spectrum [1]. Although congenital defects are often loosely considered to be primarily genetic mistakes, the evidence suggests that many of these problems arise from faulty development and, therefore, are potentially reversible. A tiny esophageal primordium poses an obvious obstacle to a primary esophageal repair; however, only the signal is required to effectively restart the well-orchestrated and complex three-dimensional organ development. The signal for the growth and development of organs and tissue is often a biomechanical stimulus, and in the case of long gap EA, axial tension provides it [1, 2].

This biological approach also opened up related questions which needed answers. The questions included the quality of the esophagus recently subjected to catch up growth, the characteristics of the gastroesophageal (GE) junction, as well as the universal debates which surround the treatment of GE reflux (GER). Because strictures frequently developed at the anastomotic site, this response also needed improved understanding. All of these issues can be viewed as biological questions, and the answers will be important to designing effective therapy.

What had started as essentially a surgical monograph on EA was greatly expanded to contain chapters about all of the disorders of the esophagus and stomach in childhood. The book now features the wide variety of medical approaches to these problems as well as providing expanded surgical techniques which emphasize the underlying biological principles. As a result of this comprehensive approach, the possible obstacles to unfavorable long-term outcomes may be recognized and overcome. For pediatric caregivers, long-term outcomes leap well beyond the 5- or 10-year results common in the adult world to a goal of 70 good years, making the active pursuit of normalcy necessary.

The editors have designed this book on esophageal and gastric disorders in infants and children to be of value to all workers in this area, even the most experienced and knowledgeable. To be sure, this is a lofty goal, and to accomplish it, we have greatly increased the breadth and depth of this book. Certainly, more and more information is becoming available in each field making it difficult

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to keep up in one's own specialty much less in other areas. The selection of the best treatment plan, however, requires some understanding of the benefits and consequences of the various options even though they may be outside of one's specialty. Our experience has also indicated that there is less and less shared understanding between pediatricians and surgeons despite protestations from the "best" centers that this is "not true at our place". A medical or a surgical therapy will likely have benefits, especially initially, but limitations may appear over the long term, increasing the importance of the treatment decision.

An insightful presentation of diseases and treatments is also of real value because, currently, a world-wide consensus and uniform approach to these problems often does not exist. Even for common problems such as GER and despite the efforts of many workers in the field and attempts to provide well-reasoned recommendations, little seems to be settled in the minds of practitioners. The assessment and treatment of GER is surprisingly varied among pediatricians and surgeons, as well as between them. Esophageal strictures also remain unsettled, and we have found that individual conclusions about the severity of the findings and the resulting treatment plans vary widely not only across the world but even within institutions. The chapters in this book also reveal that disagreements may exist even among those knowledgeable and experienced. Understanding should be improved, however, by fully presenting the issues which will help practitioners achieve more logical treatment plans.

The goal of 70 years requires an active pursuit of normalcy. For the goal to be reached, follow-up evaluations and treatments are often required to be sure normalcy does not slip away. Well-designed clinical studies with longer follow-up will be expected and, eventually, demanded by families as well as practitioners. At present, while evidence-based decision-making is certainly a worthwhile goal, it is in limited supply. We anticipate that the authors of this book will continue to be leaders in developing well-designed studies which will contribute to the evidence base; in the meantime, however, practitioners must select and provide treatment based on the information available. The contents of this book will aid making these decisions.

The biological underpinning of the clinical situations is of particular importance for pediatric problems. The developmental abnormalities of many congenital defects exist against an active background of continuing normal development, which greatly increases the complexity. Whether medical or surgical, any therapy which affects development over a long period will likely have consequences. The commonly used acid suppression treatment of reflux esophagitis, for example, may produce significant effects on the development of the acid-producing cells. Other effects may be more distant, and the proton pump inhibitors, for example, may alter calcium metabolism and slowly lead to decreased bone density. Such considerations become greater the longer the planned therapy. What might seem to be routine treatments with defined consequences in the adult population may be of far greater significance in the developing infant and child.

Surgical treatments may also have significant later consequences. A thoracotomy incision which results in the fusion of ribs and/or the loss of innervation of the serratus anterior muscle predictably leads to significant chest wall problems which may include scoliosis. Certainly, the various interposition grafts for long gap EA often have increasing problems with time, and these should be considered when selecting the initial therapy. Granted, no current operation is in its final form, but the principles and details that comprise the surgical indications and goals as well as the long-term outcomes should be accessible and part of the therapeutic considerations. Because operations in children are carried out against the background of growth and development, the longer view will be more and more thrust upon surgeons.

For those caring for children, there almost seems to be an assumption that life does not go much beyond age 16; a proposition for which there is little evidence. The teenager is handed off "doing well" to practitioners caring for young adults and, in effect, disappears from the pediatric world. The long-term consequences of GER, for example, and the later effects of other therapies used in childhood, whether medical or surgical, illustrate the importance of the longer view.

Treatment unfortunately may require a choice between a relatively easy short-term solution and one that appears more difficult initially but which has significant long-term advantages. This conflict is most often present in surgical approaches. An operation which produces a desirable short length of stay (LOS) does not necessarily place the child on a path to 70 good years. The latter goal may be an unwelcome burden for the surgeon whose peace of mind as well as reputation depends on a shorter LOS and the occurrence of only well-recognized and "acceptable" complications. Currently, problems which may occur 20 or 30 years later might not even be considered. The spread of information and the inevitable increasing emphasis on long-term results, however, will make these considerations necessary.

The therapy of difficult lesions and diseases may also run the risk of setting in motion new problems or the substitution of one disease state for another. Palliative solutions are sometimes necessary but, by definition, bring their own chronic issues, and, with time, the deficiencies will become more important. Transplantation, with the need to hold off rejection, provides a clear example of the problems that predictably result from substituting one chronic disease for another. Interposition grafts for EA, as mentioned, significantly alter anatomy and function and the later consequences are often unsatisfactory. Palliation, although sometimes necessary, will likely be less frequently used.

This book also provides detailed explanations, which are not readily available elsewhere, of the surgical treatment of some of the most severe problems. Growth induction provides a good solution to the difficult problem of LG-EA, but there are technical demands in achieving a good end result. The details helpful in growth induction as well as in the surgical treatment of related problems are presented. As our practice has shown, a number of complications can result even from routine EA/TEF repairs as well as from other esophageal and gastric operations. Consequently, the surgical topics include the difficult esophageal anastomosis, the long stricture, the recurrent TEF, a large diverticulum, the partial intrathoracic stomach, significant tracheomalacia, and various re-operative strategies. Pediatric surgeons will recognize the biological solutions to many of these problems are a departure from current approaches. Because the objectives are more nearly normal anatomy and function, however, they should be considered. The surgical descriptions will overcome the space and page limitations of journal articles and should be helpful.

When a principle is basic and effective, it is likely to have other general applications with improved treatment solutions. Although not applicable to every problem, there are other examples of tissue or organ deficiency where growth induction has been used with impressive results. Deficiencies of skin and abdominal wall are commonly treated with tissue expanders to aid closure. These devices were initially thought to involve only skin stretching, but basic studies have shown a proliferative response to the tension by the many cell types involved [3]. For patients with a hypoplastic cardiac ventricle, increased flow across the AV valves induced growth and produced two usable ventricles [4]. Longitudinal tension has induced growth of the small intestine experimentally [5]. Traction has lengthened intra-abdominal testes and allowed a normal location [5]. For these problems of organ deficiencies, as previously with LG-EA, the traditional treatments have been palliative or otherwise unsatisfactory for the long term. The use of biological solutions and the induction of normal development have moved the outlook for these patients far closer to normal.

Of additional biological interest is that in these applications of growth induction, the stimulus is variable which may be important to a maximum response. Although the biomechanical growth signal is increased at intervals, the strength wanes as growth occurs. The importance of variable signal strength to maximize growth has been more rigorously demonstrated in cell culture experiments [6]. Interestingly enough, this important observation was made first, although not fully recognized in the clinical treatment of LG-EA.

As stated at the beginning of the Introduction, the goal in pediatric therapy must be for 70 or

more good years, and this is a stringent requirement. The problems encountered in pediatric patients are a complex mixture of developmental and genetic defects, which play out with a continuing background of normal and abnormal development. The aim of this book is to clarify as much as possible these complex interactions to guide the therapeutic options. Treatments which enlist normal biological responses, we believe, will have particular value [7]. As this approach becomes better understood and the applications expand in number, the goal of 70 good years will come into view for even the more difficult of these problems.

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Part II

The Esophagus

2 The Genetics and Molecular Biology of Oesophageal Development

Stephen P. Robertson and Spencer W. Beasley

Epidemiology

Incidence

The incidence of EA/TEF has been measured in three large epidemiological studies drawn from populations in Europe and California and from a worldwide collaboration [3–5]. These studies identified a relatively invariant incidence ranging between 2.55 and 2.86 cases per 10,000 births. The proportion of cases defined as isolated EA (in contrast to those with one or more additional congenital malformations) ranged from 38.7 to 57.3 %. All three studies included cases complicated by chromosomal anomalies. It is likely that exclusion of early foetal deaths in the international study, many of which would be associated with multiple additional malformations, has led to an overestimate of the proportion of EA that is truly isolated in nature and accounts for some of the variation in these estimates between the three studies. In all three cohorts, there was a male preponderance of cases ranging from 52 to 62 % of the total sample. Of all infants with EA/TEF, 50 % have associated congenital anomalies. Many represent the presence of a syndrome for which mutations in a single gene of major effect are responsible (see below) or represent instances of a recognised association, the primary mechanistic basis of which has not been defined.

Effect of Parity and Birth Weight

Extremes of parity and low birth weight are both associated with EA/TEF [6]. The malformation is over-represented in prematurely born infants although the explanation for this may partially lie in concomitant obstetric complications (e.g. maternal polyhydramnios) that frequently complicate such pregnancies and can precipitate premature labour.

Twinning

The rate of twinning is increased in association with EA (7 % vs 2.3 % in the Royal Children's Hospital, Melbourne study) [7–9]. Additionally twins are at an elevated risk (2.56-fold; 95 % CI 2.01–3.25) of having EA although such twin pairs will generally be discordant for the malformation (concordance rate 2.5–4 % [6, 9]).

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The interpretation of these data is, as is the case with many congenital anomalies, that twinning itself seems to constitute a risk factor although the biological basis for this phenomenon is poorly understood. In one study [9], mean birth weight, gestational age and survival were lower in twin infants with EA/TEF compared to affected singletons. Similarly, congenital anomalies were also over-represented in this group.

Teratology

Although exposure to certain medications and infections during pregnancy has been proposed as a possible risk factor for the development of EA/TEF, no external factor has been consistently linked to its development [10]. Candidate teratogens that may result in EA/TEF include mycophenolate mofetil [11], methimazole [12] and related agents such as carbimazole [13] that may lead to a specific embryopathy which includes EA/TEF [14, 15]. It is noteworthy that carbimazole exposure is also associated with choanal atresia and colobomata – both major criteria for a diagnosis of CHARGE syndrome, a monogenic disorder that is also associated with EA/TEF [16, 17]. This observation would be consistent with a mechanistic basis for the teratogenic effect of these antithyroid drugs that involves the gene mutated in CHARGE syndrome, *CHD7* (see below) and/or cellular components that relate directly to its function as a chromatin-modifying protein.

Despite the lack of clear causal links with environmental agents in humans, the successful development of a mammalian model for EA using the administration of Adriamycin to pregnant rats raises the possibility that EA/TEF could result from teratogenic exposure in humans.

The Genetics of Oesophageal Atresia

It is convenient to divide EA/TEF into two groups: those presenting with EA/TEF as part of a syndrome, the so-called syndromic esophageal atresia (SEA), and those individuals in whom EA/TEF is an isolated abnormality and not part of any syndrome – isolated esophageal atresia (IEA). It must be acknowledged that although this categorisation may be useful for epidemiological purposes, SEA can initially present as IEA in a family due to the wide clinical variability associated with some of the syndromic entities that include EA/TEF as a phenotypic component.

Recurrence Risk

For individuals with isolated EA/TEF without a clear aetiology, the recurrence risk for sibs for the same malformation is less that 1 % [1, 18, 19]. No comparative data for recurrence risks for isolated versus non-isolated EA/TEF are available, although the relevant recurrence risk for some aetiologies (e.g. aneuploidy, monogenic syndromes) is well established. This fact underscores the importance of seeking as precise a diagnosis as possible for all infants with syndromic or non-isolated EA/TEF and the limitations of treating these designations as a homogeneous group. Due to several decades of improving surgical and postoperative management of infants with EA/TEF, figures are becoming available that estimate the risk to offspring of individuals with TEF. In this instance, the recurrence risk is, like the sibling recurrence risk, also in the region of 1 % [18], providing further evidence that genetic factors do not play a substantial role in the cause of EA/TEF.

Although the recurrence of EA/TEF itself is low, there is evidence that first-degree relatives of individuals are at an elevated risk of associated anomalies. For individuals with EA/TEF without a clearly defined aetiology, the recurrence risk to first-degree relatives for EA/TEF or for a wide spectrum of malformations that fall within the VACTERL group of anomalies (see below) is elevated twofold over the general population risk figure [19, 20]. These estimates apply to offspring of individuals with both isolated and non-isolated EA/TEF but importantly exclude those with a clear chromosomal or Mendelian aetiology.

Genetic Syndromes

An identifiable syndrome underlies the presentation of EA/TEF in approximately 50 % of cases. These genetic entities include Mendelian syndromic disorders, segmental chromosomal aneuploid states and trisomy for several chromosomes. For several of these Mendelian disorders, a causative gene has been identified and a substantial amount is known of the developmental pathways in which some of these operate (see below). Tellingly, however, no genetic factors have been identified that contribute to isolated, non-syndromic EA/TEF, reflecting the epidemiological evidence that genetic factors are not predominant in the causation of non-syndromic forms of this malformation.

The study of syndromic EA/TEF with a confirmed genetic aetiology in conjunction with experiments in animal models has done the most to advance understanding of the biology of EA/TEF over the last 20 years. For example, in those instances of EA/TEF where an underlying genetic aetiology has been defined, no confirmed association has been identified between these genetic etiological categories and the five subtypes of EA/TEF (A–E) [1] defined on anatomical grounds. This suggests that these subtypes represent a disruption at various stages on a continuum to which multiple genetic and environmental factors contribute.

Chromosomal Disorders Associated with EA/TEF

In complete surveys of fetuses and infants with EA, 6–10 % of cases will have a chromosomal anomaly that is visible on G-banded karyotypic analysis [3–5]. The commonest aneuploid states that are associated with EA include trisomy 18 and trisomy 21 [21–24]. In terms of absolute risk, the incidence of EA complicating trisomy 18 is greater (~25 % of all individuals with trisomy 18) than that in trisomy 21 (~0.5–1.0 % of individuals affected with trisomy 21) [21–24]. EA has been reported as a much less frequent accompaniment of trisomy 13 and trisomy 8 mosaicism.

Segmental Chromosomal Imbalance

Segmental chromosomal aneuploidy refers to a group of conditions that are characterised by chromosomal imbalance (either a duplication or deletion) that is less than an entire chromosome in extent. The identification of such imbalances as correlated with certain specific malformations can serve as a useful first approximation of the whereabouts of single genes that lead to the same phenotypic effect when disrupted. Several loci characterised by recurrent imbalance that is frequently (but not always invariably) associated with EA/TEF have been identified. The non-random occurrence of these associations indicates the existence of specific genes that when mutated will lead to EA/TEF in a proportion of individuals – although the phenotypic result, as noted above, tends to be a syndromic presentation of EA/TEF rather than isolated disease [21].

The most frequently observed segments of chromosomal imbalance that have been observed in association with EA/TEF are:

- Deletions of 2q37.2-qter [25], 3q27-ter, 4q35-qter, 5p15-pter, 6q13-q15, 12q24-ter [26], 13q34-qter, 14q32.3-qter, 17q22-q23 [27, 28] and 22q11 [29, 30]
- Duplications of 3p25-pter and 5q34-qter

Additionally other chromosomal anomalies have been reported that may also give some indication to the location of genes predisposing to the development of EA/TEF:

- Patients with deletions on 13q present with anomalies resembling the VACTERL association within which EA/TEF is represented.
- A chr 6;15 reciprocal translocation disrupting the *BPAG* gene has been studied in a single patient with neurodevelopmental disability and EA [31].

Genetic Syndromes with a Defined Monogenic Aetiology

The definition of chromosomal regions and aneuploid states can give a broad indication that genetic factors play a role in the etiopathogenesis of oesophageal atresia. However, defining exactly what genes and pathways play a direct role in

humans has been difficult, at least until the relatively recent description of the genetic basis of several Mendelian disorders that feature EA/TEF as a prominent phenotypic component. Several genes involved in syndromic forms of EA/TEF that are inherited in an autosomal dominant fashion have been identified recently (*N-MYC*, *SOX2* and *CHD7*). Only one recessively inherited entity (Fanconi anaemia) demonstrates EA/TEF as a recurrent (albeit still infrequent) component of its presentation. Two X-linked disorders also have EA/TEF as a presenting feature and indicate that their underlying genes play a role in the partitioning and canalisation of the upper aerodigestive tract.

Autosomal Dominant Syndromic EA/TEF (Table 2.1)

Anophthalmia-Esophageal-Genital (AEG) Syndrome (MIM 206900)

AEG syndrome is an autosomal dominant multiple malformation syndrome characterised by anophthalmia/microphthalmia, EA/TEF and anomalies of the urogenital tract (cryptorchidism, hypospadias and hypogentialism). Mutations in *SOX2* are responsible [32]. Patients with point mutations in *SOX2* can also manifest hearing loss and variable degrees of psychomotor retardation. Chromosomal anomalies encompassing this locus, as well as point mutations and intragenic deletions, indicate that the mode of action of these mutations is via haploinsufficiency for the SOX2 protein. SOX2 is a transcription factor that has established roles in organogenesis, most notably in the eye [33], in the hypothalamic-pituitary axis and in the differentiation of epithelium in the developing aerodigestive tract. Murine expression of *Sox2* is highest in the developing foregut endoderm which develops to form the future oesophagus and stomach. Mice whose *Sox2* has been selectively deleted from the anterior epithelial field of the developing anterior foregut have defective epithelial-mesenchymal interactions and tracheal branching in addition to EA/TEF [34, 35].

CHARGE Syndrome (MIM 214800) [36, 37]

This multiple malformation syndrome is clinically defined by the presence of major and minor criteria. The major criteria for diagnosis include the presence of colobomata of the eye, heart anomalies, atresia of the choanae, retardation of mental and somatic development, genital hypoplasia and ear abnormalities and/or hearing loss. Although not a major criterion, EA/TEF is present in approximately 10 % of cases [36, 38]. CHARGE syndrome usually presents as a sporadic disorder in families, but occasional parent-child transmissions have been recorded. The genetic basis of nearly all cases of the condition is mutation in the chromodomain-helicase DNA-binding domain-containing protein, *CHD7*. Mutation types include point mutations, intragenic deletions and whole-gene deletions [1, 36, 37, 39]. The function of *CHD7* is to regulate the transcriptional activity of broad arrays of genes in a reversible

Table 2.1 Autosomal dominant syndromes with assigned genes associated with EA/TEF

Syndrome	Gene	Locus	Clinical manifestations
Anophthalmia-oesophageal-genital syndrome	*SOX2*	3q26.3	Anophthalmia/microphthalmia, EA/TEF urogenital tract anomalies
CHARGE syndrome	*CHD7*	8q12.1	Ocular colobomata, cardiac anomalies, choanal atresia, mental and growth retardation, genital anomalies, auditory anomalies
Feingold syndrome	*MYCN*	2p24.1	Oesophageal and duodenal atresia, microcephaly digital anomalies, cardiac defects

manner during development through epigenetic modification of heterochromatin [40]. Upon the description of *CHD7* as the underlying causative gene in CHARGE syndrome, it was anticipated that understanding the targets that are regulated by this protein would indicate genes and pathways that are subverted to lead to the multiple malformations in diverse organ systems in this condition. At this time, few such targets have been defined [40].

Feingold Syndrome (MIM 164280)

This autosomal dominant condition is characterised by variable combinations of gastrointestinal tract atresia, the two principal forms being oesophageal and duodenal atresia. Anorectal malformations have also been described [41]. The syndrome also features microcephaly, learning disabilities, digital anomalies and cardiac defects [42]. The digital anomalies, although seldom incapacitating, can be characteristic and in conjunction with EA/TEF are highly suggestive of the diagnosis. These anomalies include brachydactyly due primarily to shortening of the middle phalanges of digits 2 and 5. Clinodactyly of the same digits together with syndactyly of the toes also occurs. Individuals with Feingold syndrome are heterozygous for mutations and deletions of *N-MYCN* [43]. *N-MYC* is a regulator of the hedgehog signalling pathway, a set of genes that are activated widely throughout multiple organ systems in development including the brain, heart and developing limb in addition to the foregut. The discovery that mutations in this gene lead to EA was therefore congruent with the findings in the rat that hedgehog signalling is dysregulated in drug-induced EA (see below). Notably, point mutations in *N-MYC* were only observed in exons incorporated in full-length *NMYC* transcripts [44], indicating that domain-specific functions were at the heart of the pathogenesis of this condition. A knockout mouse model of the gene orthologous to human *N-MYC* produced multiple malformations, but not EA as is seen in the Feingold syndrome [45].

Oesophageal Atresia/ Tracheoesophageal Fistula in Recessively Inherited Syndrome

Fanconi Anaemia (Table 2.2)

Fanconi anaemia is characterised by bone marrow failure, short stature, skin pigmentary anomalies, hearing loss, developmental delay and a wide variety of congenital malformations that can include radial ray, eye, renal, cardiac and central nervous system anomalies. Gastrointestinal anomalies, including EA/TEF, are observed frequently. Due to their close similarity in clinical presentation, it is not uncommon for sporadic presentations of Fanconi anaemia to be misdiagnosed as the VACTERL association. It is essential that Fanconi anaemia is definitively excluded in infants who appear to have the VACTERL association because of its markedly different natural history and recurrence risk [46].

Mutations in all but one of the genes implicated in the causation of Fanconi anaemia are associated with autosomal recessive inheritance. The exception is the *FANCB* locus which is located on the X chromosome. An X-linked subtype of VACTERL association has been described that incorporates hydrocephalus as a clinical manifestation and is caused by mutations in the *FANCB* gene [47].

X-Linked Syndromic EA/TEF (Table 2.3)

Opitz syndrome is characterised by midline abnormalities including cleft lip, heart defects, hypospadias, agenesis of the corpus callosum and laryngeal clefts. Occasionally EA/TEF is observed, although laryngotracheal clefts are the most commonly occurring malformations in the tracheoesophageal complex [48]. Mutations in *MID1* lead to the syndrome [49]. The pathophysiological connection between *MID1* and other pathways implicated in EA may lie with its role in asymmetrically distributing Gli transcription factors in the early developing embryo [50, 51].

VACTERL association with hydrocephalus (VACTERL-H) is characterised by vertebral anomalies, anorectal malformations, cardiac malformations, EA/TEF, renal and limb anomalies

Table 2.2 Autosomal recessive syndromes with assigned genes associated with EA/TEF

Syndrome	Genes	Clinical findings
Fanconi anaemia	*FANCA*, *FANCB*,*FANCC*, *FANCD2*,*FANCE*, *FANCF*,*FANCG*, *FANC*,*BRIP1*, *FANCL*,*FANCM*, *PALB2*	Bone marrow failure, predisposition to malignancy, short stature, abnormal skin pigmentation, radial ray limb anomalies, renal and cardiac defects; developmental delay gastrointestinal anomalies including EA/TEF

Table 2.3 X-linked syndromes with assigned genes associated with EA/TEF

Syndrome	Gene	Locus	Clinical findings
Opitz syndrome	*MID1*	Xp22	Cleft lip, laryngeal clefts, heart defects, hypospadias, EA/TEF (rare)
VACTERL-H	*FANCB*	Xp22.31	Vertebral anomalies; anal atresia; EA/TEF; renal, cardiac and limb anomalies; hydrocephalus

and hydrocephalus. Mutations in the *FANCB* have been associated with this phenotype [47].

Genetic Syndromes with an Undefined Genetic Aetiology

Several other syndromes currently defined by their clinical presentation have had EA/TEF reported as a phenotypic component in a variable number of instances:

- A syndrome incorporating supernumerary nostrils, EA and persistent ductus arteriosus [52]
- A syndrome incorporating EA, hypoplasia of the zygomatic arch complex, mental retardation, congenital heart defects and microcephaly [53]
- Martinez-Frias syndrome (multiple gastrointestinal tract atresias; MIM 601346)
- Bartsocas-Papas syndrome (lethal multiple pterygium syndrome; MIM 263650)

Fryns syndrome (diaphragmatic hernia, coarse facies, digital anomalies; MIM 229850)

Associations

An association is a non-random co-occurrence of clinical features without evidence for them being collectively caused by a defined single etiological factor. Associations differ from syndromes in that the co-occurrence of clinical manifestations in syndromes is due to an identifiable shared cause that can be either environmental or genetic or a combination of both.

VATER/VACTERL Association (OMIM 192350)

This is defined as the non-random association of *v*ertebral, *a*nal, *c*ardiac, *t*racheoesophageal fistula, *r*enal and *l*imb defects. It was initially described as the VATER association, but subsequent, more rigorous attempts to define which malformations are genuinely associated with each other (as opposed to representing artefacts of ascertainment) led to extending the association to include cardiac and limb defects. Approximately 10% of infants with EA/TEF have at least two of the other defects included in the VACTERL spectrum and can be said to have VACTERL association if a specific syndromic diagnosis cannot be reached [54]. Nearly one half of individuals with EA/TEF will have malformations in the VACTERL spectrum of anomalies [19], a fact ascribable to the considerable overlap between the forms of malformation that co-occur in defined syndromes and those also found as a component of the VATER/VACTERL spectrum. Although the sibling recurrence risk for VACTERL is low and familial occurrences rare,

first-degree relatives of individuals with EA are at elevated risk of having malformations within the VACTERL spectrum, an observation that is consistent with ill-understood genetic determinants contributing to the VACTERL spectrum of anomalies [19, 20]. Moreover, mice with mutations in genes within the Shh and Gli pathways demonstrate malformations within the spectrum of VACTERL anomalies, hinting that signalling by these genes is involved in the pathogenesis of these malformations.

Schisis Association

This condition represents a non-random association of neural tube defects with exomphalos (omphalocele), oral clefts and posterolateral diaphragmatic hernia [55]. An elevated incidence of oesophageal atresia has been noted in association with neural tube defects in experimental animals, but whether EA/TEF is also over-represented in similar instances in humans remains to be established.

Molecular Biology of Oesophageal Atresia

Until recently, embryologists have largely concerned themselves with detailed description of the changes that occur in the morphology of the growing embryo, and the vocabulary of embryogenesis has been that of cell differentiation, differential cell growth, body layers folding, fusion and division. With advances in genetics and molecular biology, interest has increasingly focused on the processes that occur at a cellular level and gene patterns of expression and elucidating gene signalling pathways. The following pages are devoted to some recent observations that have contributed to our understanding of the molecular biology of the embryogenesis of the foregut and its derivatives at the molecular level.

Early Development of the Foregut

Following gastrulation, the definitive endoderm becomes the primitive gut tube, of which the most cranial (anterior) region is known as the foregut. Its early morphogenesis is determined by transcription factor genes such as *Foxa 1*, *Foxa 2*, *Gata 4* and *Gata 6* that are expressed in the endoderm [56–58]. Their local expression along the anteroposterior (AP) axis of the foregut endoderm marks organ-specific domains (specifically thyroid, thymus, trachea, lung, liver and pancreas). For example, the homeodomain protein gene *Nkx2.1* (*also known as Titf1 or T/EBP*) is expressed in the thyroid and respiratory fields [59].

At critical times, the primitive foregut also receives diffusible signals from adjacent structures whose proximity changes according to changes in the shape and relationships of the embryo, and this too influences endodermal cell specification [60, 61]. Fibroblast growth factor 4 (Fgf 4), bone morphogenetic protein 2 (Bmp2) and retinoic acid (RA) are among the signals that confer AP identity to the early endoderm and enable it to respond to signals from both adjacent mesoderm and nearby structures [56, 62].

The early development of the respiration system and its separation from the gut and the genes that control the processes are summarised in Table 2.4.

Primary Lung Bud Morphogenesis

In mice, lung buds form at E9.5 (25 somite stage) in a process initiated by the local expression of a Fgf ligand (*branchless*) where the budding will occur, followed by activation of a Fgf receptor (*breathless*) that induces budding [64]. In mammals, signalling by Fgf10 and Ffgr2b is crucial for lung bud formation [56], and deletion of either results in lung agenesis. Fgfr2b is the major receptor for Fgf10.

Tracheoesophageal Separation

Embryologists have long recognised that clarification of the processes that surround normal tracheoesophageal separation was critical to a better understanding of the abnormal separation of the trachea from the oesophagus that leads to EA/

Table 2.4 Stages in the development of the respiratory system from the primitive foregut

1. Two endodermal lung buds (precursors of the left and right bronchi) are induced from the ventral-lateral aspect of the single foregut tube [56]
Nkx2.1-expressing endodermal cells are the first respiratory progenitors to appear
Lung budding initiated by expression of signalling molecules, such as Fgfs and local transcription factors
In mammals, signalling by Fgf10 and Fgfr2b crucial for lung bud formation
Likely additional roles for RA, Gli2, Gli3, Tbx2, Tbx3 and Tbx4
2. Ventral tracheal primordium separates from the dorsal aspect of the foregut (precursor of the oesophagus) by apoptosis
Influenced by *Shh* and *Nkx2.1* (and probably *Foxf1*, *Tbx4*, *RA*)
3. Secondary budding of lung buds into specific bronchi and into separate lobes to form the respiratory tree
Nkx2.1 required for expression of several lung markers, including *Sftpc* [63]
Fgf10 triggers secondary and subsequent budding
Local downregulation of the Sry-like HMG box transcription factor *Sox2* may be required for lung budding
BMP4 prevents distal epithelial cells assuming a proximal phenotype

TEF. Many theories of the pathophysiology of EA/TEF have been proposed but even the two theories that have held most sway have recently been challenged [65]. One theory, the "tap water" theory [66–68] states that the respiratory bud forms from the primitive pharyngeal wall and descends in a way similar to that of a tap being turned on: first the trachea develops after which the bronchi appear and develop. The second theory, the "tracheoesophageal septum" theory [69, 70], describes how fusion of two lateral tracheoesophageal ridges separates the trachea from the oesophagus. These ridges form a septum that ascends to the pharynx to complete the process of separation, leaving the trachea ventrally and oesophagus dorsally.

Whilst these theories do not accommodate all observations, they do reflect several aspects of early tracheoesophageal separation and have served as useful models. In the mouse and rat, there is now clear evidence that the bronchi develop as "lung buds" before tracheoesophageal separation occurs (Fig. 2.1), a process probably driven by Fgf10 expressed in the mesenchyme overlying the tips of the primary buds [71]. The "tap water" theory assumes that the trachea develops first as an out-pouching from the foregut tube, which then elongates caudally and later divides into lung buds. As it does so, it and the later developing lung buds appear to descend from the primitive pharyngeal floor. This interpretation may not be exactly accurate but is based on the correct observation that the distance between the point of tracheoesophageal separation and the pharynx alters little during the period of development. Progressive caudo-cranial apoptosis on the lateral walls of the foregut maintains the point of separation, the same absolute distance from the pharynx despite ongoing growth of both the fetus and the foregut (Fig. 2.2), [65]. Although the point of tracheoesophageal separation commences immediately cranial to the future gastro-oesophageal junction, apoptosis in the lateral walls of the foregut causes it to remain the same distance from the pharynx throughout its relative ascent to the sagittal laryngeal lamina during this critical phase of development.

What controls this process of tracheoesophageal separation? Bmp4 is expressed in the ventral mesoderm in the region which will subsequently become the trachea, whereas noggin is expressed in the dorsal endoderm of the foregut in the region that later becomes the oesophagus. The noggin protein may protect the dorsal endoderm from the action of Bmp4 [72].

Patterns of Apoptosis During Tracheoesophageal Separation

There are three processes that determine morphology during early embryogenesis:

1. Differential rates of cell division, i.e. the relative rate of increase in the numbers of specific cells and the space they occupy influences morphology

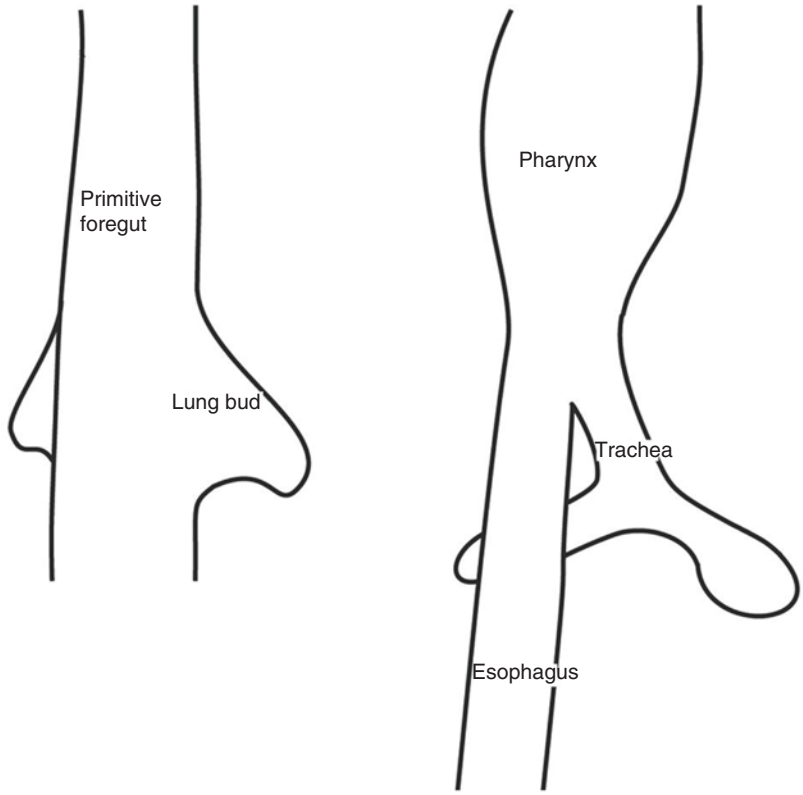

Fig. 2.1 In the rat (and mouse), the bronchi develop as "lung buds" before tracheoesophageal separation occurs and before the lung itself develops. The figure shows the changes that occur during lung bud development in the rat between gestational day 11.5 and day 12

2. Cell differentiation – the type of cell
3. Apoptosis (programmed cell death) where cells that have been present, but are no longer required, disappear

Apoptosis is tightly controlled and occurs at a specific time and at a specific location, i.e. it has strict temporo-spatial characteristics. Anything that alters its timing or location markedly changes the ultimate morphology of the affected organ.

Apoptosis appears to be critical in ensuring appropriate tracheoesophageal separation. In the primitive foregut of the normal rat, apoptosis occurs in the lateral walls at the point of tracheoesophageal separation on day 12 (Fig. 2.3), but in the Adriamycin-exposed rat that is developing oesophageal atresia, it fails to occur at this time [72]. The foregut remains a single tube in that region and has features more in keeping with a trachea, with connections to the lungs. Ultimately, an upper oesophageal pouch develops from the posterior wall of the pharynx (see below). The normal pattern of apoptosis is disturbed in the Adriamycin-exposed rat model of oesophageal atresia [73] as well as in the Shh and Nkx2.1 mouse models of foregut malformations [74].

Subsequent Branching of Lung Buds

Branching of the respiratory tree is controlled by a complex exchange of signals between the buds themselves and the surrounding mesenchyme. These determine the size and shape of the bud during branching [56].

Fgfr2b activity and *Fgf10* expression are controlled by the sprouty (Spry) and Shh

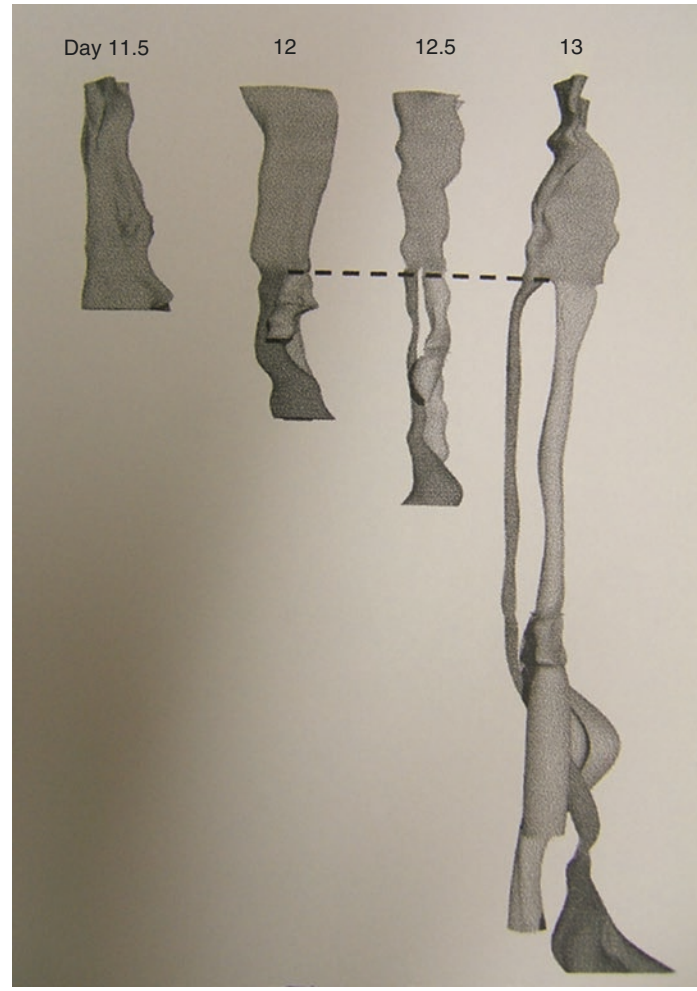

Fig. 2.2 During tracheoesophageal separation in the rat, there is progressive caudo-cranial apoptosis on the lateral walls of the foregut which maintains the proximal point of separation of the trachea and oesophagus, the same absolute distance from the pharynx – despite ongoing growth of both the fetus and the foregut

pathways, respectively. Fgf10 diffuses locally to bind to Fgfr2b, which is expressed throughout the lung epithelium, and activates induction of a further bud. Fgfr2b signalling induces expression of *Spry2* and *Bmp4* which have an inhibiting effect.

Shh signalling in the disal mesenchyme inhibits *Fgf10* expression but via Gli3 also controls availability of Foxf1, a positive regulator of *Fgf10* [56]. By induction of *Hhip* expression, Shh also inhibits its own signalling to allow *fgf10* expression. Low Shh levels in the more proximal bud regions allow *fgf10* expression in adjacent mesenchyme, enabling later induction of the lateral buds [56].

A number of other genes have been implicated in lung branching as well, but their exact role remains unclear. Bmp4 probably works through its ability to influence Fgf10-mediated bud outgrowth [56]. The role of Wnt signalling is controversial: several Wnt ligands, frizzled receptors and components of the Wnt pathway (e.g. β-catenin and Tcf/Lef transcription factors) are present in the developing lung [75]. Tgfb1, Tgfb2 and Tgfb3, members of the Tgfb subfamily, also affect lung branching [56], and exogenous Tgfb1 inhibits branching [76].

Expression of the transcription factor Foxf1 in the foregut mesoderm is partly regulated by Shh signalling through Gli3 [77]. It appears to be upregulated by Shh protein and inhibited by Bmp4 [78]. Heterozygous *Foxf1* embryos have a narrow oesophagus abnormally connected to an irregular and very abnormal trachea [72].

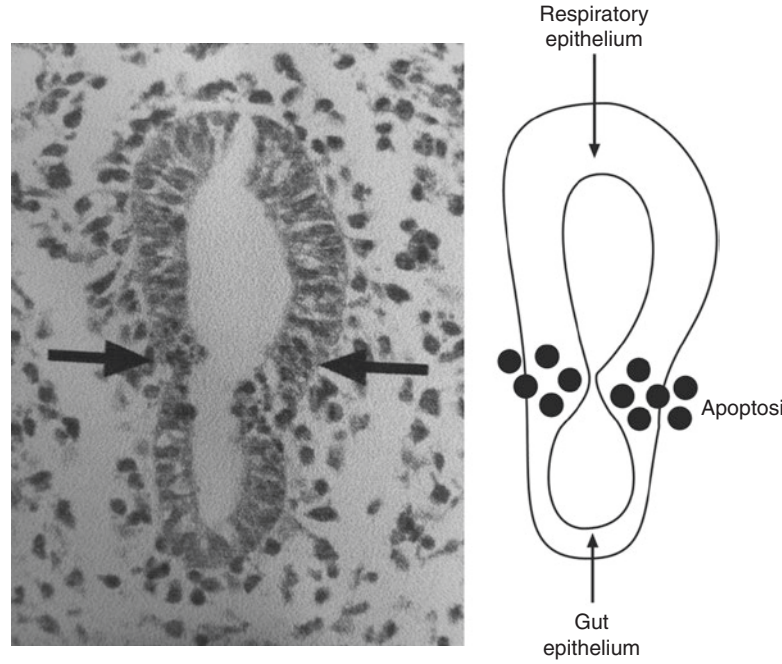

Fig. 2.3 In the normal rat, apoptosis occurs in the lateral walls at the point of tracheoesophageal separation on day 12 (unlike in the Adriamycin-exposed rat that is developing oesophageal atresia where it fails to occur at this time, and the primitive foregut remains a single tube). During normal development, apoptosis of the lateral walls of the primitive foregut effectively splits the tube into an anterior respiratory tube (which becomes the trachea) and a posterior tube (which becomes the oesophagus)

The Proximal Oesophageal Pouch

The development of the proximal oesophageal pouch in oesophageal atresia has never been well understood. The appearance of the upper oesophageal segment does not fit comfortably with many theories of embryogenesis of oesophageal atresia. Moreover, differences in its cellular properties [79] and in its innervation and intrinsic nerve supply [79, 80] have not always been easy to explain. Finally the proximal oesophageal pouch appears to elongate after birth, further fuelling the debate [81]. Recent research indicates that apoptosis plays a role in the development of the proximal oesophageal pouch, at least in the rat [82]. Apoptosis in the dorsal wall of the pharynx is the first indication of upper pouch development, and this is followed by proliferation of the cells immediately dorsal to this point. Proliferation and extension of the proximal oesophageal pouch continues until day 16 of gestation [82].

In the human, the proximal oesophageal pouch in oesophageal atresia is usually relatively long when there is a distal tracheoesophageal fistula. In contrast, the proximal oesophagus in rats with oesophageal atresia elongates and grows caudally from day 15, but for how long this growth occurs in late gestation and after birth is uncertain. It is conceivable that in the human with oesophageal atresia, growth of the upper oesophagus may continue to occur during the remaining 30 weeks of gestation and even after birth. This would be consistent with the clinical observation that the proximal oesophageal pouch appears to elongate significantly after birth, irrespective of whether bougienage is performed [81].

Development of the Notochord in Oesophageal Atresia

The notochord acts as a primary organiser in normal embryogenesis [83] and is involved in directing the formation of the neural tube, sclerotome and myotome [84]. It runs along the embryonal axis between the endoderm and ectoderm from the third week of gestation. Later it degenerates, except for those parts that persist as the intervertebral discs. Abnormal development of the notochord produces abnormalities of the vertebral column, ribs, limbs and neuroenteric canal

remnants. The notochord of rat embryos exposed to Adriamycin [85, 86] or *Nog* null mutants [72] becomes malpositioned. The vertebral bodies fail to develop properly, resulting in hemivertebrae. In these embryos, the notochord often has an extremely bizarre and abnormal branching pattern and may be split [85–88]. In rats developing oesophageal atresia, the notochord often becomes abnormally adherent to the foregut and assumes a grossly abnormal and distorted shape with branching (Fig. 2.4) [85, 89]. The more the notochord is abnormal, the more disturbed is subsequent foregut development, and the more likely there will be abnormalities of the vertebral column, including hemivertebrae [90].

In Adriamycin-exposed rats developing oesophageal atresia, *Shh* is expressed profusely in the abnormal ventral branches of the distorted notochord, including where it is abnormally adherent to the foregut (normally it has no direct contact with the foregut). The notochord has been shown to be a major source of signalling activity influencing the development of cell populations in the tissues that surround it. For a molecular messenger, which acts in a dose dependent and diffusible manner in organising

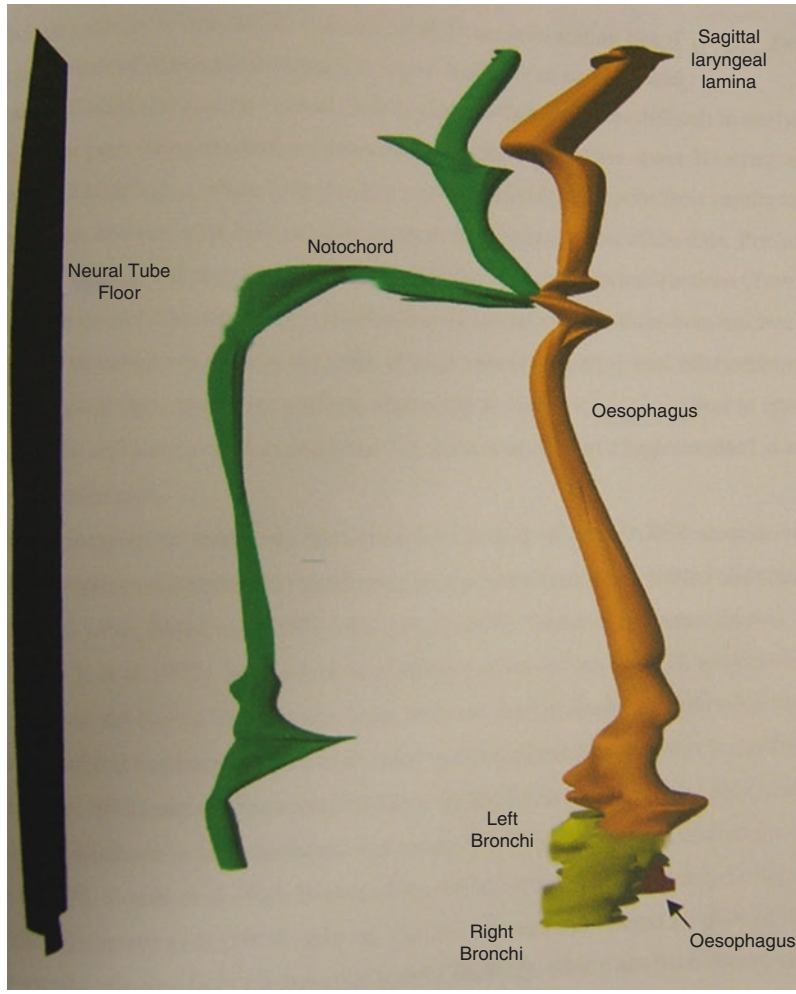

Fig. 2.4 In rats developing oesophageal atresia, the notochord often becomes displaced well anterior to its usual position and in one or more parts can become abnormally adherent to the foregut. Overall, it assumes a grossly abnormal and distorted shape and often has an abnormal branching pattern (Modified from Williams et al. [85])

patterns of early development, it is likely that the ectopic expression of *Shh* (in relation to the primitive foregut) and its actual distance from the target tissue may lead to interference with normal development [91].

The temporal and spatial characteristics of expression of *Shh* gene in the foregut are different between the normal embryo and those embryos that are developing oesophageal atresia [91] (Fig. 2.5). Normally, the *Shh* gene is expressed strongly in those parts of the foregut that eventually become the trachea (the anterior aspect of the primitive foregut), whereas the expression in those parts of the foregut epithelium that later become oesophagus (the posterior aspect) is either absent or comparatively low. In Adriamycin-exposed rats that appear to be developing oesophageal atresia, the usual pattern of dorsal-ventral *Shh* expression is lost [91] and those with abnormal diffuse expression are likely to develop structural abnormalities [92]. In short, expression of *Shh* in the foregut is abnormal when the position of the notochord is abnormal. A possible consequence of the abnormal proximity of the notochord to the foregut is that the foregut expression of *Shh* may be repressed by excessive signals from the notochord.

It is noteworthy that the notochord of *Nog* null mutants that are developing EA/TEF is also grossly abnormal, whereas the small proportion of Nog null mutants that do not develop EA/TEF have a normal notochord [72]. It is likely that Noggin normally functions by restricting the level of the Bmp4 signalling in the dorsal foregut region; thus, the notochordal abnormalities observed may reflect the requirement for correct levels of Bmp signalling during separation of the notochord from the endoderm. Reducing the dose of *Bmp4* markedly reduces the risk of EA/TEF in *Noggin* null mutants [72].

Further research is required to confirm whether Shh from the notochord promotes *Nog* expression in the dorsal foregut endoderm. If this were so, the EA/TEF seen in Shh null mutants (as also occurs after exposure of rat embryos to Adriamycin) may be due to an imbalance in Bmp4 signalling [72], at least in part.

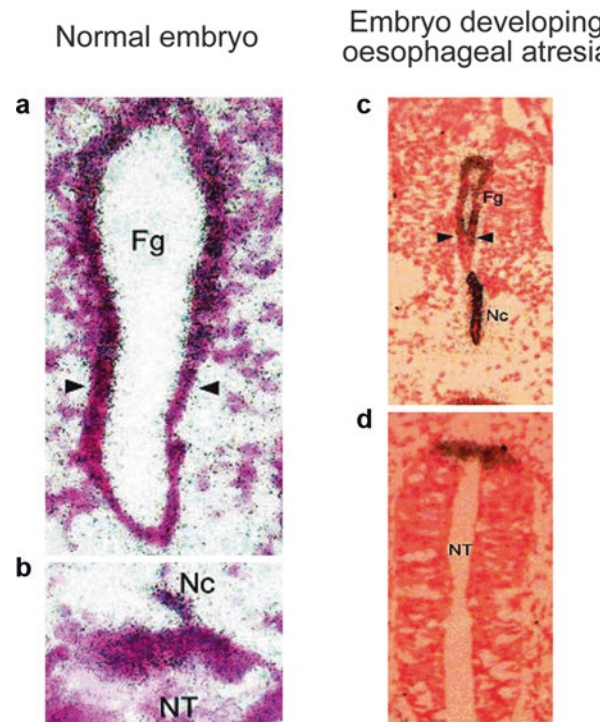

Fig. 2.5 The temporo-spatial characteristics of *Shh* expression in the foregut are tightly controlled. The black dots identify the location of Shh expression in the normal rat embryo (**a**, **b**) and in the rat embryo developing oesophageal atresia (**c**, **d**). Note also the anterior displacement and abnormal attachment of the notochord to the foregut in the Adriamycin-exposed embryo in which oesophageal atresia is occurring

Sonic Hedgehog in Organogenesis

Normal expression of *Shh* begins just after the establishment of the digestive tube [93, 94] and continues throughout the development of the gut. *Shh* exhibits its regulation in a concentration-dependent manner. *Shh* expression is first present during early development when it maintains the epithelium. Later in gut development, it is involved in the region-specific differentiation of epithelium and mesenchyme [95–97], and this is reflected in its specific timing and location of expression [74]. Levels of *Shh* gene and protein during normal development of the foregut in rat embryos are different from those that are developing oesophageal atresia [98]. Normally, Shh protein is expressed in the rat foregut throughout embryogenesis, and its level declines as the embryo approaches birth. In Adriamycin-exposed rats that are developing oesophageal atresia, the level of Shh protein expression is much lower than normal and varies little with time [98] (Fig. 2.6), providing further evidence that disruption of the Shh signalling pathway leads to abnormal development of the foregut.

The overall importance of Shh in organogenesis is highlighted by the observation that disruption of normal *Shh* expression during critical periods of development is associated with not just abnormalities of the foregut and hindgut but holoprosencephaly (HPE) and the VACTERL association as well. An autosomal form of HPE has been shown to be associated with mutations in human *Shh* coding sequences [99]. This observation in the human applies also to the *Shh* −/− mouse.

Hedgehog proteins are secreted as inactive precursor proteins that undergo post-translational modification. One part (the N-terminal) remains associated with the surface of the cells, whereas the other (the C-terminal peptide is freely diffusible [100]. This enables *Shh* to direct long-range effects (such as sclerotome differentiation – the precursor of vertebrae and ribs) as well as short-range effects (neural tube development) [99]. Patched (*Ptc*) is the receptor for *Shh*. In the absence of hedgehog, Ptc receptors block the

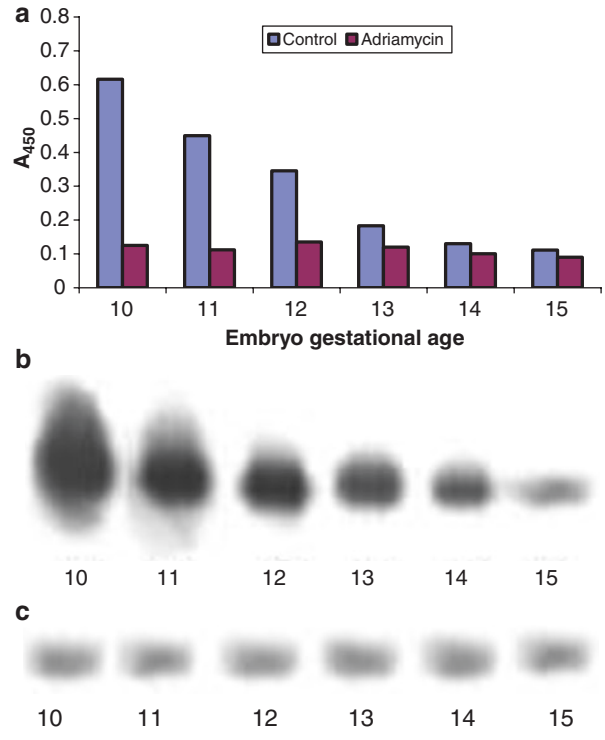

Fig. 2.6 Levels of Shh protein during normal development of the foregut in rat embryos are different from those that are developing oesophageal atresia. (**a**) ELIZA test confirms the presence of Shh protein (Santa Cruz antibody) in foregut homogenates and shows that its level decreases significantly over time, whilst Adriamycin exposure results in a diminished level of Shh protein without time-dependent changes. Immunoblot demonstrates that cleaved amino-terminal Shh signal protein in both the normal rat embryo (**b**) and the rat in whom oesophageal atresia is developing as a result of Adriamycin exposure (**c**) between the critical gestational days 10 and 15 (Modified from Arsic et al. [98])

function of another protein, Smoothened (Smo), and inhibit signalling. When the hedgehog is bound to Ptc, Smo becomes active and initiates a signalling cascade that results in the activation of three Gli transcription factors, Gli1, Gli2 and Gli3 [101]. In turn, the Gli transcription factors are responsible for the activation and repression of several hedgehog target genes, including tumour growth factor (TGF-β), cyclins, p21, β-catenin, bone morphogenetic protein (BMP) and fibroblast growth factor family (FGF) (Fig. 2.7). In the absence of *Shh*, Gli proteins translocate to the nucleus where they act as the main transcriptional repressors of the target genes.

Evidence from the Shh, Nog and Nkx2.1 Null Mutant Mouse Models

In the wild-type mouse embryo, the trachea begins to separate from the oesophagus by a "tracheoesophageal septum", whereas this septum does not appear in the *Shh* $^{-/-}$ mutant embryos, implicating *Shh* in the separation of the respiratory tube from the digestive tube in this model [95, 102].

Knockout mutant mice (for Gli1, Gli2, Gli3) have been produced to elucidate the role of the various Gli genes in sonic hedgehog signalling [51]. Gli $3^{-/-}$ mutant mice have many abnormalities, including central nervous system and lung defects, and limb polydactyly [101]. Aspects of these phenotypes are similar to *sonic hedgehog* gain of function. Gli $2^{-/-}$ mutant mice die at birth with severe skeletal and neural defects. The normal mouse lung develops with four right lobes and one left lobe, whereas the right lung in the Gli $2^{+/-}$ mutant has only one lobe. The size of the lung in Gli 2 $^{-/-}$ is significantly reduced, the oesophagus does not develop smooth muscle and the oesophageal lumen is small. Gli 2/Gli 3 double-mutant mice have been used to demonstrate the overlapping functions of Gli 2 and Gli 3 in foregut development. Gli $2^{+/-}$ Gli $3^{+/-}$ mutant mice are viable without obvious foregut defects, whereas Gli $2^{-/-}$ Gli $3^{+/-}$ mutants have oesophageal atresia with a tracheoesophageal fistula. In these mutants, the single foregut tube does not

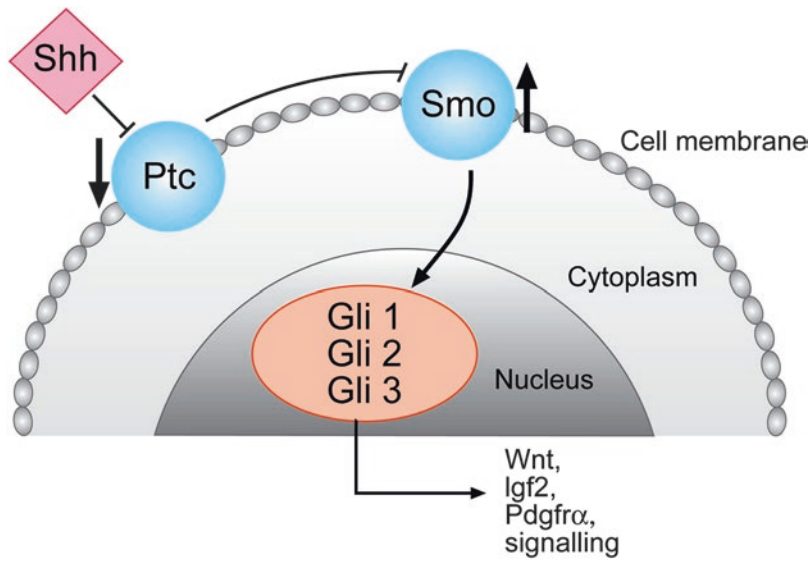

Fig. 2.7 The *Shh*-Gli pathway. Sonic hedgehog (*Shh*) acts on the membrane receptor complex consisting of Patched (Ptd) and Smoothened (*Smo*) to inhibit the repression of Smo by Ptc. Smo signals the cell causing the GLI proteins in the nucleus to regulate target genes, including tumour growth factor (TGF-β), cyclins, p21, β-catenin, bone morphogenetic protein (BMP) and fibroblast growth factor family (FGF) In the absence of *Shh*, Ptc receptors block the function of another protein, Smoothened (*Smo*), and inhibit signalling

separate normally into the trachea and oesophagus [51]. Interestingly, Gli 1 functions as dispensable in mice if both copies of the Gli 2 gene are present [101]. These findings are consistent with the observation that mice with a targeted deletion of *Shh* and *Gli* mutants develop oesophageal atresia and related abnormalities because of breakdown of the *Shh* signalling pathways [103].

In the mouse at E9.5, the homeodomain transcription factor *Nkx2.1* is expressed in the ventral foregut endoderm in the region where the trachea and lungs will develop [104]. This is controlled by Ffgs (and probably other factors such as RA as well). Null mutations in Nkx2.1 compromise tracheoesophageal separation [104], although in the absence of an oesophageal pouch, normal dorsoventral patterns of Nkx2.1 and Sox2 expression have been observed in Adriamycin-exposed mouse embryos who have defective foregut separation [74].

Deletion of the human chromosomal region containing the NOGGIN gene can produce EA/TEF [28]. More recent work confirms that *Nog* null mutants also have EA and TEF. The close functional interrelationship of these genes is evident in that *Nog* encodes a polypeptide of Bmps. Also, *Nog* and *Bmp4* are reciprocally expressed in distinct and specific dorsal and ventral domains in the foregut [74].

In summary, *Nog* mutants resemble *Shh* and compound *Gli* mutants (and embryonic exposure to Adriamycin) in producing EA/TEF and its variants [74].

Future Directions

The enormous advances that have occurred in recent years in both clinical genetics and molecular biology have given researchers tools that will continue to provide new insights into the complex processes and effects of gene expression on morphology. A better understanding of normal processes will assist us in identifying how and why aberrations of normal development occur – aberrations that sometimes lead to oesophageal atresia and its related abnormalities. One might hope that eventually this knowledge will be applied to the prevention of these conditions.

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Swallowing and the Upper Esophageal Sphincter

3

Robert E. Kramer

Introduction

Swallowing is a complex physiologic process, requiring integration of both voluntary and involuntary motor complexes within both the respiratory and digestive systems. Alterations in this process may present with a wide variety of clinical manifestations, including aspiration, chronic cough, choking, dysphagia, feeding problems, vomiting/retching, oral aversion, and failure to thrive. Evaluation of swallowing disorders can be challenging and difficult to differentiate from respiratory, neurologic, allergic, developmental, or other gastrointestinal disorders. In many patients there may be two or more of these processes occurring simultaneously, making it difficult to ascertain the primary pathology or the relative contribution of each. This challenge is made more difficult in infants and toddlers who are unable to communicate details about their symptoms that can help pinpoint the root of the problems. Furthermore, the dynamic transition in diet that occurs during the first year of life, in terms of taste, consistency, and mode of feeding, is yet another layer of complexity which may obfuscate swallowing and behavioral feeding disorders. Addressing these patients, therefore, often requires a multidisciplinary approach, with input from gastroenterologists, occupational or speech therapists, dietitians, radiologists, and other pediatric specialists, such as pulmonologists and otolaryngologists. In order to understand the myriad ways that this process can go awry, a thorough understanding of the normal process of swallowing is essential.

Normal Swallowing

The purpose of swallowing is to propel the contents of the oral cavity, including secretions, liquids, and solids, through the oropharynx and hypopharynx, past the upper esophageal sphincter (UES) into the esophagus and ultimately into the stomach for digestion. Swallowing can be functionally divided into an oral phase and a pharyngeal phase.

Oral Phase

In the oral phase, initiation of swallowing occurs following appropriate mastication (for solids) and bolus control by the tongue. This is a voluntary process controlled by the central nervous system. The tongue accommodates bolus size and prepares the bolus for swallowing by

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approximating the posterior portion of the tongue to the soft palate, effectively separating the bolus from the hypopharynx and airway. This bolus activates receptors within the oropharynx, which provide sensory information to the swallowing center by virtue of afferent nerve fibers coursing through branches of the trigeminal, glossopharyngeal, and vagus nerves. The swallowing center integrates this information to determine that the bolus is appropriate for swallowing. Swallowing is then voluntarily initiated in conjunction with cessation of respiration, opening of the UES, and peristalsis in the striated portion of the upper esophagus.

In the first specific step in this process, the mouth is closed, the tip of the tongue is pressed against the hard palate, and the lateral aspect of the tongue is pressed against the alveolar ridges, forming a seal. A wave of contraction then occurs from the tip through the body of the tongue, propelling the food bolus from the oral cavity into the oropharynx, completing the oral phase of swallowing [1].

Pharyngeal Phase

Within the pharyngeal phase of swallowing, several events occur in a near simultaneous fashion. The base of the tongue pushes bolus posteriorly, while the oropharynx is elevated and pushed open. Meanwhile, the extrinsic muscles, comprised of the levator veli palatini, tensor veli palatini, palatoglossus, and palatopharyngeus muscles, close the nasopharynx off from the food bolus by elevating the soft palate and uvula. Other extrinsic muscles such as the stylohyoid, styloglossus, stylopharyngeus, and digastric posterior raise the larynx while the geniohyoid, mylohyoid, digastric anterior, and thyrohyoid pull the larynx and pharynx forward, helping to open the UES. The intrinsic muscles, comprised of the superior, middle, and inferior pharyngeal constrictors, are responsible for creating negative pressure in front of the bolus, while it is pushed from behind by the action of the tongue, resulting in advancement of the bolus into the esophagus. The inferior pharyngeal constrictor is comprised of two parts, the thyropharyngeus and the cricopharyngeus, which forms part of the UES. At this point, the bolus is intersecting the airway, and measures must be taken to protect it. Therefore, the thyroarytenoid, aryepiglottic, and the oblique arytenoid close the larynx to block off the trachea.

The primary peristaltic wave is initiated in the pharynx and extends through the cervical portion of the esophagus. Liquids progress primarily by gravity in the upright position and typically reach a closed lower esophageal sphincter (LES) before the peristaltic wave. Solid boluses travel by virtue of gravity as well as peristalsis, which opens the LES and permits passage into the gastric lumen. Secondary peristaltic waves may occur locally, by virtue of the enteric nervous system, in response to distention from residual food content within the esophagus [1]. Between swallows, the UES and the LES remain tonically contracted to minimize gastroesophageal and esophagopharyngeal reflux, respectively.

Neurologic Control of Swallowing

Coordination of the complex steps involved in normal swallowing, as outlined above, requires the integration of sensory data from the periphery to modulate motor control. This control is mediated through the parasympathetic, sympathetic, and enteric nervous systems. Integration and control of the parasympathetic system occurs primarily within the swallowing center, located in the dorsal vagal complex. The dorsal vagal complex sits within the dorsomedial hindbrain medulla and encompasses two nuclei, the nucleus tractus solitarius and the dorsal motor nucleus. Vagal afferents, carrying sensory information from the pharynx, esophagus, and stomach synapse within the nucleus tractus solitarius. This information is then projected to the nucleus ambiguous to coordinate the process of deglutition and to the dorsal motor nucleus of the vagus, which sends motor output to the esophagus. The rostral and caudal portions of the dorsal motor nucleus each provide opposing influences on lower esophageal sphincter pressure, with the

rostral portion causing contraction and the caudal causing relaxation. Thus, the resulting tone of the LES is the balance of these two influences.

The sympathetic control of swallowing function arises in the intermediolateral columns of the thoracic spinal cord, at the level of T1 through T10. The majority of the preganglionic fibers pass through the greater splanchnic nerves to terminate in the celiac ganglia. Postganglionic neurons then travel to the esophagus via perivascular fibers to synapse in the myenteric and submucosal plexi of the esophagus.

Local innervation of the esophagus via the enteric nervous system arises within the complex network of submucosal (Meissner's) and myenteric (Auerbach's) plexi. Though this system receives input from and provides feedback to the central nervous system, it is capable of producing secondary peristalsis even with complete dissociation from the CNS [2]. Its effects are modulated by release of nitric oxide, as well as other neuropeptides from nerve endings, which are differentially expressed along the length of the esophagus [3]. In the circular muscle layer, the concentration of nitrous oxide (NO)-containing neurons decreases along the length of the esophagus, with the lowest amount found at the level of the LES. In the longitudinal muscle layer, this pattern is reversed, with greatest concentration of NO-containing neurons at the LES. This pattern suggests that peristalsis in the esophagus is modulated by the release of inhibitory neuropeptides and NO along its length [4].

Upper Esophageal Sphincter

The UES is a functional zone of high pressure demarking the entrance to the esophagus. It has two primary functions. The first is relaxation, to accommodate passage of a solid or liquid bolus into the esophagus following deglutition or to allow expulsion of gas during belching. The second is contraction, to prevent entry of air into the esophagus during inspiration and passage of refluxate into the pharynx. This zone of high pressure is variable in length, extending up to 4 cm in adults and exhibiting radial asymmetry, with greatest pressures in the anterior and posterior aspects. The muscles responsible for UES opening are the thyrohyoid and the geniohyoid, while those responsible for closure are primarily the cricopharyngeus and to a lesser extent the thyropharyngeus and cervical esophagus. The UES at rest is retained in a state of tonic contraction, due to continuous firing of medullary neurons, running through the vagal trunks. Cessation of firing leads to UES relaxation, while rate of firing determines the resting pressure. The range of normal resting pressure for the UES is difficult to establish due to variability in testing methods, the radial asymmetry of UES pressure, and the stimulatory effect of recording instruments. In adults the normal range is estimated to be between 40 and 100 mmHg.

The deglutition process, described above, leads to almost immediate UES relaxation to a pressure level equivalent to that of the pharynx, though cessation of neural input from the brainstem. This relaxation in pressure alone, however, is not sufficient to allow opening of the UES. It is accompanied by elevation and forward displacement of the larynx, which serves to pull open the UES. This relaxation immediately precedes pharyngeal contraction, facilitating the transport of the food bolus from the hypopharynx into the upper esophagus. This brief relaxation lasts less than 1 s.

A number of factors can alter resting UES tone, in accordance with the primary functions it performs. To prevent or minimize entrance of air into the esophagus during respiration, tone increases during inspiration, while thoracic and esophageal pressures decrease. To minimize pharyngeal passage of refluxate, acid exposure in the proximal esophagus increases UES tone as well. Similarly, balloon distention in the proximal esophagus, modeling liquid refluxate, also results in increased tone. Exposure of the mucosa to water or neutral liquids does not produce as pronounced of an increase as does acid. Conversely, balloon distention modeling passage of gas results in a decrease in UES tone, to accommodate belching. This relaxation is paired with glottis closure to further protect the airway. The mechanisms used to discriminate gaseous versus

liquid distention are not well characterized. Animal data suggest that the response to acid exposure is modulated via vagal afferents in the recurrent laryngeal nerves. This pathway only seems to be responsible for a portion of the response to esophageal distention, however. Patients with peptic esophagitis do not appear to have any alteration or impairment of this normal pathway. Emotional stress seems to increase UES tone, which may be involved in globus sensation. During deep sleep, UES tone decreases, which may be a factor in nocturnal gastroesophageal reflux. Anesthesia virtually eliminates UES tone, increasing the risk for aspiration of gastric contents during procedures in patients with an unprotected airway.

The cricothyroid muscle is responsible for the majority of UES tone, and impaired relaxation results in a high-pressure bar across this region. This is clinically defined as cricopharyngeal achalasia. In cricopharyngeal achalasia, there is also impaired distensibility of the cricopharyngeus, which forms the appearance of a "bar" from its indentation during a barium swallow. The impaired ability to open the UES during deglutition results in increased bolus pressure in the hypopharynx, which can lead to a Zenker's diverticulum. This is a false diverticulum created at an area of pharyngeal weakness between the oblique fibers of the inferior pharyngeal constrictors and the cricopharyngeus muscle itself. Diverticulae may also occur at the junction of the middle and inferior constrictors. These diverticulae may result in trapped food content, a sensation of dysphagia and risk for aspiration. In contrast, paralysis of the suprahyoid pharyngeal constrictors results in paralytic achalasia due to failure of UES opening (Table 3.1).

Table 3.1 Factors affecting resting upper esophageal sphincter tone

Increased tone	Decreased tone
Inspiration	Deep sleep
Emotional stress	Deglutition
Distention from liquids	Belching/distention from air
Acid exposure	Emesis

Oropharyngeal Dysphagia

Assessment

Dysphagia is defined as "difficulty swallowing" and is contained within the broader category of feeding disorders. Feeding disorders in general are relatively common in the pediatric age group, estimated to occur in up to 45 % of children with normal development and 80 % in those with developmental disabilities [5]. With the improved survival of premature infants over the last few decades, the resultant incidence of children with developmental deficits has increased and with it the incidence of feeding/swallowing disorders.

Identification of children who warrant a formal evaluation by a feeding team can be challenging from the primary care perspective. Arvedson has developed a panel of questions which can aid the caregiver in determining whether a given patient has reached that threshold (see Table 3.2) [6]. These patients require a multidisciplinary approach to successfully discriminate the organic and nonorganic components, which are often inextricably entwined. Commonly, underlying feeding or swallowing disorders result in compensatory measures or strategies in parents which may become maladaptive and cause oral aversion. This has led to a proposed set of criteria for the formal diagnosis of "feeding disorder between parent and child" which recognizes this issue [7].

Paramount in importance during the evaluation of these children is an accurate assessment of the risk of continued oral feedings and implementation of appropriate measures to provide for safe delivery of adequate nutrition. In the primary assessment period, anatomic and obstructive lesions must first be excluded. A comprehensive medical history must be obtained, as virtually any primary neurologic disorder or muscular disease involving the oropharynx can result in dysphagia. Deficits in either afferent or efferent innervation of the oropharynx can result in dysfunction by interfering with the intricate timing of the swallowing processes outlined above. Potential points where dysfunction can occur

Table 3.2 Screening assessment for feeding team referral

Question	Assessment
How long does it take the child to feed?	More than 25–30 min points to a problem
Is the child totally dependent on others for feeding?	Children unable to self-feed in an age-appropriate manner are at increased risk for feeding problems and silent aspiration
Does the child refuse food?	Food refusal may be an indication of disordered parent-child interaction, sensorimotor deficits, or underlying organic disease
Are mealtimes stressful?	Increased parental stress with meals can lead to forced feedings and subsequent oral aversion in the child
Has the child slowed or stopped growing in the previous 2–3 months?	Growth delay points to significant impairment of the ability to provide adequate nutrition in the face of the observed feeding problems
Are there signs of respiratory distress?	Increase suspicion of aspiration
Does the child vomit regularly?	Points to underlying organic pathology, such as reflux, obstruction, impaired motility, or others. In some cases, children may vomit purposefully as a method of food refusal
Does the child become irritable or lethargic during meals?	Fussiness with feeds may indicate underlying inflammation or irritation within the upper GI tract, as well as airway issues. Lethargy my indicate fatigue from inefficient or difficult feeding

include tongue loading, bolus propulsion, nasopharyngeal closure, laryngeal closure, UES opening, and pharyngeal clearance. Regardless of the underlying cause or mechanism, dysphagia in infants and children is significantly correlated to the risk of aspiration pneumonia [8].

Etiology

The potential etiologies for feeding problems and dysphagia in infants and children are numerous and often interrelated. Anticipatory guidance must be given for patients with known risk factors for feeding disorders so that appropriate feeding strategies can be implemented and nutrition can be delivered in a safe fashion. Though certainly not exhaustive, the potential etiologies outlined below constitute some of the most common causes seen in the pediatric age group.

Prematurity

The premature infant faces a number of challenges that may result in feeding difficulties and dysphagia. First and foremost, among these is the developmental readiness necessary to coordinate sucking, swallowing, and respiration. Although the prenatal fetus is capable of deglutition of amniotic fluid by 16 weeks gestation, it is not generally until 34 weeks post-conceptional age that suckling capability is acquired. Even at this point, preterm infants may have difficulty coordinating swallowing and breathing, which may result in aspiration with oral feeds. These problems may be compounded by other common comorbid conditions encountered in the preterm infant, such as bronchopulmonary dysplasia [9], necrotizing enterocolitis [10], and gastroesophageal reflux [11]. Prolonged use of oxygen therapy for lung disease in preterm infants may further impair development of nonnutritive suckling (NNS), due to decreased positive stimulation and increased perioral noxious stimuli from intubation and taping [12, 13]. As a result, introduction of oral feeds may be significantly delayed in these patients, causing them to miss a critical period of oral stimulation. Subsequent development of normal oral feeding may be interrupted and difficult to reestablish. Prophylactic implementation of nonnutritive suckling during gavage feeds may help avoid these pitfalls [14] and seems to result in decreased hospital stay and improved transition from tube feeds to bottle feeds [15].

Cerebral Palsy (CP)

Neurological dysphagia can be related to a number of conditions, but cerebral palsy is by far the most common [16]. The mechanism for dysphagia in these patients may be related to

hypertonicity, hypotonicity, abnormal suckling and rooting reflexes, and sensory changes to oral stimuli [17]. Swallowing disorders in these children can be grouped into three primary categories [18]. In the first, there are significant oromotor difficulties, such as tongue thrusting and poor lip closure, resulting in impaired control of the food or liquid bolus within the oropharynx. In the second, there are the same oromotor issues, with the addition of delayed initiation of the pharyngeal phase of swallowing. This pattern seems to be the most commonly encountered in patients with cerebral palsy. In the third, both the oromotor problems and the delayed pharyngeal swallowing are accompanied by inefficient pharyngeal clearance following the swallow. Impaired opening of the UES and cricopharyngeal dysfunction are uncommon in CP patients, so that aspiration *during* the swallow is unusual. Aspiration, if present, typically occurs *before* the swallow due to poor oromotor control or *after* the swallow due to poor pharyngeal clearance of the food bolus.

Genetic Syndromes

Congenital birth defects and genetic syndromes are commonly associated with feeding and swallowing disorders. In these conditions the dysphagia can be related to one or more problems impacting feeding. Central nervous system dysfunction causing generalized hypotonia is a common element in many of these congenital disorders which result in impaired feeding. Anatomic abnormalities of the nasopharynx, such as submucosal cleft, macroglossia, cleft lip/palate, and micrognathia, can disrupt normal suckling and latching in the feeding infant. Neurological compromise can result in dysfunctional swallowing by interrupting the timing or efficiency of the normal swallowing process. A list of some of the more common genetic conditions associated with feeding and swallowing disorders is presented in Table 3.3 [19].

Neuromuscular Disease

Essentially any neuromuscular disease which involves the swallowing musculature can result in dysphagia. Myotonic dystrophy is a characteristic example, in which there is impaired relaxation of affected muscle. Pharyngeal and esophageal abnormalities are near universal in these patients, resulting in weakened pharyngeal contraction and decreased or absent peristalsis within the esophagus. These patients are at risk for aspiration, as difficulty in passing the food bolus through the cricopharyngeus results in overflow of the pyriform sinuses which may cause retained contents to fall into the opened airway after the swallow [18]. Spinal muscular atrophy type II results in oromotor problems with retained food in the valleculae, as well as swallowing dysfunction [20]. Recent data suggests that feeding function in these patients may be improved if the head is tilted forward during feeding [21].

Postsurgery/Congenital Heart Defects

Vagal nerve injury following surgery can result in hemiparesis of the soft palate and pharyngeal constrictors, leading to possible nasopharyngeal reflux and interrupting symmetrical sweeping of the pharynx following the swallow. The recurrent laryngeal nerve can be injured during any surgery involving the thyroid or mediastinum. The left recurrent laryngeal nerve is more vulnerable than the right, as it creates a larger loop within the chest. Injury to the nerve may result in unilateral vocal cord paralysis, leaving the airway vulnerable to aspiration. This increased risk has been studied in patients who have undergone surgical correction of congenital cardiovascular defects, where subsequent vocal cord dysfunction was found in 1.7 % [22]. The risk was greatest in those patients undergoing aortic reconstruction, and more than half required gastrostomy placement to manage their long-term feeding difficulties. Clement et al. found PDA ligation to be associated with a greater than 50 % incidence of vocal cord paralysis, with increased risk in extremely low birth weight infants, and associated with increased requirements for tube feeding and ventilator support [23].

Other associated conditions leading to oropharyngeal dysphagia include tracheostomy, due to decreased elevation of the larynx [24], medullary tumors such as medulloblastoma [25], and

Table 3.3 Genetic syndromes commonly associated with feeding/swallowing disorders

Syndrome	Characteristic feeding issues
Angelman syndrome	Frequent feeding problems but not severe
Apert syndrome	Related to cleft palate feeding issues
Arthrogryposis	Aversion to solids, swallowing problems
ATR-X syndrome	Hypotonia, poor suck
Beckwith-Wiedemann syndrome	Macroglossia with feeding problems
CHARGE syndrome	Pharyngeal incoordination, abnormal laryngeal and pharyngeal anatomy
Cornelia De Lange syndrome	Poor oral coordination, small mouth and jaw
Costello syndrome	Poor suck with severe feeding problems
Deletion 22q13 syndrome	Mild problems, secondary to hypotonia
Down syndrome	Tongue hypotonia, small oral cavity, poor suck
Fragile X syndrome	Feeding problems common but no dysphagia
Holoprosencephaly	Significant problems, poor suck, possible aspiration, may have cleft lip/palate
Kabuki syndrome	Feeding problems in up to 70 %, poor coordination of suck and swallow
Myotonic dystrophy type 1	Weakness of facial and pharyngeal muscles
Noonan syndrome	Poor suck, prolonged feeding time
Prader-Willi syndrome	Infantile hypotonia, leading to poor suck
Rett syndrome	Delayed pharyngeal swallow
Robin sequence	Difficulty maintaining airway while feeding
Rubinstein-Taybi syndrome	Hypotonia, feeding problems in 80 %
Smith-Lemli-Opitz syndrome	Hypotonia and poor suck commonly lead to feeding problems commonly
Smith-Magenis syndrome	Infantile hypotonia, poor suck and swallow, oral sensorimotor dysfunction
Soto syndrome	Failure to suck, poor coordination of swallowing
Treacher Collins syndrome	Craniofacial malformations/cleft lip/palate
Trisomy 18, Trisomy 13	Poor suck and swallow
Turner syndrome	Difficulty latching to breast and suckling
Velocardiofacial syndrome	Nasal regurgitation due to hypoplastic soft palate with large nasopharynx, poor esophageal peristalsis, risk of aspiration
Williams syndrome	Severe feeding problems in 70 %, sensory aversion to solids, tongue thrust, abnormal position of jaw and neck
Wolf-Hirschhorn (4p-) syndrome	Central hypotonia, orofacial clefts, results in poor suck

traumatic brain injury, with dysphagia prevalence as high as 76 % [26].

Evaluation

Feeding Observation

Despite the numerous radiologic, endoscopic, and functional diagnostic tests available for feeding evaluation, there is nothing that replaces careful observation of the affected child during an actual feed. This is usually performed by a speech-language pathologist or occupational therapist. Before the formal evaluation occurs, the astute observer should take care to assess the patient at rest, before feeding actually begins. Careful attention should be paid to facial symmetry, presence of dysmorphic features, size and position of the tongue, and appearance of the lip and palate. In the infant, observation of nonnutritive sucking ability may give early clues as to the proficiency of nipple feeds. If the NNS does not appear vigorous and rhythmic, the infant may have difficulty coordinating suck, swallowing, and breathing with sufficient ease to provide adequate nutrition. After the global assessment is complete, the true feeding observation can take place but should be performed in a venue that most closely approximates the usual home feeding environment. It is important that the observa-

tional period is of sufficient duration to determine that a representative sample is witnessed and that late feeding fatigue or disorganization is not missed. Usual feeding should not require more than 30 min to complete.

Feeding characteristics observed during the assessment may give important clues to underlying dysfunction. Cranial nerve abnormalities may be suspected on the basis of these observations. Cranial nerves V, VII, IX, X, and XII are all involved in feeding and swallowing function, and impairment of these cranial nerves (CN) causes distinctive feeding abnormalities [6]. For example, CN V dysfunction results in inability to form a food bolus, while CN VII problems may result in poor lip seal and movement. CN IX and X dysfunction results in delayed initiation of the pharyngeal swallow after food is loaded in the posterior oropharynx. Typically this action should be initiated within 2 s of the bolus being moved posteriorly within the oropharynx. CN XII abnormality results in poor tongue elevation and excessive thrusting. Another important clue is the need for multiple swallows to completely clear the pharynx, indicating impaired function of the pharyngeal constrictors. Abnormal movements during feeding, such as jaw thrust, tonic bite reflex, and jaw clenching, should be noted. Close observation of the parent-child interaction during feeds is critical as well. Children should be challenged with foods of varying texture. The most critical assessment that must be made at the conclusion of the feeding observation period is whether the child can safely tolerate oral feeds. Presence of a wet, coarse voice or cry following feeding should alert the clinician that aspiration may be occurring. Secondarily, the assessment may address whether modifications can be made to diet composition, timing of feeds, position, or posture to improve feeding tolerance.

Upper GI

The role of an upper GI series or esophagram is primarily focused on assessment of upper gastrointestinal anatomy. It may be helpful to determine if there are any structural anomalies which may be manifesting as feeding difficulties or dysphagia. This would include esophageal strictures and webs, vascular rings and slings, tracheoesophageal fistula, achalasia, hiatal hernia, pyloric stenosis, malrotation, and more. Though upper GI series is often requested as part of the assessment of gastroesophageal reflux, it is neither a sensitive or specific screening test for reflux [27]. It also does not adequately assess swallowing function as obtained by a true videofluoroscopic study.

Ultrasound

Ultrasound examination of the tongue, floor of the mouth, and pharynx during feeding can give a dynamic picture of the movement of these structures to help identify sites of pathology [28]. Though acoustic shadowing from bones in the neck may limit visualization, lack of radiation exposure offers an advantage over traditional fluoroscopic evaluation.

Nuclear Scintigraphy

Technitium-99m is used as a tracer to label ingested food or liquid during the study, in an effort to measure transit time or the presence of aspiration with feeds [29]. The tracer is not absorbed by the gut mucosa and will not stick to the mucosal surface. Sensitivity for detecting aspiration has generally been reported as poor, but it does have less radiation exposure than the fluoroscopic studies.

Videofluoroscopic Swallow Study

The videofluoroscopic study or modified barium swallow is the primary assessment tool for evaluation for dysphagia and feeding problems. It is especially helpful in differentiating oropharyngeal from esophageal dysfunction. It is typically performed with the patient upright and from the lateral position, with feeding administered by a speech-language pathologist. Oropharyngeal dysfunction can be broadly divided into four major categories on the videofluoroscopic exam: delayed initiation of pharyngeal swallowing, aspiration, nasopharyngeal regurgitation, and incomplete bolus clearance from the pharynx following swallowing. These studies are used extensively to determine the presence of aspiration with feeds, though the clinical significance of

small amounts of aspiration remains controversial. If aspiration is observed, careful note must be made of whether this aspiration occurs before, during, or after deglutition. Other specific findings can help identify corresponding swallowing disorders. For example, greater than three sucks per swallow suggests decreased suck strength or coordination. Decreased opening of the UES can be suspected on the basis of nasopharyngeal reflux, residue in the pyriform sinuses and pharyngeal pouches, or slow bolus passage through UES. The type and consistency of feeds can be altered to assess whether these "modifications" result in improved safety of oral feeding.

Fiberoptic Endoscopic Evaluation of Swallowing (FEES)

Conventional endoscopic evaluation has a limited role in the evaluation of dysphagia and feeding disorders. While it can be helpful in excluding esophageal conditions such as eosinophilic esophagitis, reflux esophagitis, and esophageal webs/strictures, it is not able to reliably assess swallowing function or motility disorders. In contrast, fiberoptic endoscopic evaluation of swallowing (FEES) allows for real-time direct visualization of swallowing function [30]. Though initially developed for adults, it has been used successfully in even premature infants [31], and does not require specialized endoscopic skills. There is, however, a standardized protocol for the tasks and assessments that should be performed as part of a formal FEES examination [32]. A laryngoscope is passed transnasally after topical anesthetic has been applied to the nares. Examination of the anatomy of the patient's nasopharynx and larynx, as well as their basic function, constitutes the initial portion of the examination. Included with this is an assessment of the symmetry and movement of these structures during a dry swallow, normal respiration, and phonation of specific words or sounds (if the patient is old enough to cooperate). The subsequent portion of the examination involves direct examination of these structures during delivery of liquids and solids of varying textures and bolus sizes. From this information, the examiner should be able to assess the underlying physiology of any identified swallowing problems and potentially offer guidance for manipulating feedings to improve the safety of oral intake.

Management

Cricopharyngeal Myotomy

For patients with isolated cricopharyngeal achalasia, with or without Zenker's diverticulum, myotomy may be considered as a potential therapy [33]. Response rates to myotomy are decreased when patient selection is generalized to include those with other or additional etiologies for their dysphagia. Ideally the candidate for myotomy should have cricopharyngeal dysfunction as the primary cause for their dysphagia, the ability to propel a bolus through the oropharynx to the level of the UES, and the ability to close the airway during deglutition. Given these parameters, response rates are quite good, though published data in children is scarce due to the relatively low incidence of this condition in the pediatric population [34, 35].

Enteral Access Device

If oral feeding is ultimately deemed unsafe or if the limitations in oral feedings result in an inability to take in sufficient volume to provide adequate nutrition, consideration must be given to placement of an enteral feeding device. In the pediatric setting, this decision can initially be a daunting subject for parents and caregivers to address. In each case the risk-benefit balance of each type of device must be carefully weighed to come to the best option for that child. For initial delivery of enteral nutrition in a relatively noninvasive fashion, nasogastric or nasoduodenal feeding tubes are often the best option. These tubes have the disadvantage, however, of potentially causing further disruption of the normal feeding/swallowing mechanism and perhaps hastening the development of oral aversion. Careful consideration must therefore be given to the anticipated duration that enteral support will be needed, and, if prolonged access will be required, discussion of the more durable devices, which bypass the nasopharynx, should occur. For the child felt to have treatable oropharyngeal dysphagia, the ability to

deliver appropriate nutrition while parents engage in the long process of feeding therapy enables the child to progress at their own pace [36]. Without access, there may be substantial pressure on the parents and the child to take sufficient caloric intake, which may be counterproductive to their therapy and encourage development of maladaptive feeding strategies [37].

Diet alteration

Comprehensive treatment of feeding and swallowing disorders typically involves intervention from a multidisciplinary team, often including a dietitian, behavioral psychologist, a speech-language pathologist, and an occupational therapist. There are numerous strategies available to alter the diet to address current feeding limitations and encourage the development of feeding skills [38]. For the infant, adjusting the nipples used for feeds can change flow rate and allow for improved function [39]. Modifying the thickness can decrease aspiration risk for patients with dysphagia to thin liquids, as determined from videofluoroscopy. For patients with sensory integration disorders leading to feeding problems, changing texture of solids may enhance palatability and acceptance.

Positioning/Timing of Feedings

For patients with specific disorders, changing position or posture with feedings may allow improved function by accentuating the portions of their swallowing mechanism that work well. For those patients with unilateral weakness of pharyngeal constrictors, turning the head to the side may improve swallowing efficiency and decrease risk of aspiration. Additional exercises to strengthen muscles of the face, tongue, lips, and palate can be prescribed for the parents to implement in the home [38]. Adjusting the pace of feeding to allow more time for swallowing may be necessary and is sometimes aided by the use of smaller utensils.

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Esophageal Motility

4

Hayat M. Mousa and Rodrigo Machado

General Background

The esophagus is a hollow viscous constituted of four layers: mucosa, submucosa, muscle layer, and adventitia. The esophageal mucosa is formed by three layers: nonkeratinizing stratified squamous epithelium, the lamina propria (with mucous glands), and the muscularis mucosa. Mucus-producing tubular glands (submucosal or esophageal glands) extending into the submucosa are scattered throughout the esophagus [1]. The submucosa is composed by loose connective tissue containing arteriolar plexus, elastic fibers, and nerve cell bodies of Meissner's plexus.

The esophageal muscle layer presents unique features, as it is composed by striated muscle in the first quarter and smooth muscle in its distal half. The second quarter is mixed, with striated and smooth (involuntary) fibers. In the internal layer, the muscle fibers are circular, while the external layer presents longitudinal fibers. The myenteric ganglia (Auerbach's) are located between these layers. These ganglia, together with those of Meissner's plexus, play an important role in the coordination of esophageal motility. The last layer, adventitia, is composed of loose connective tissue, allowing movement of the organ during swallows. Physiologically, three parts are distinguishable: the upper esophageal sphincter, the esophageal body (EB), and the lower esophageal sphincter.

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Upper Esophageal Sphincter (UES)

The pharyngoesophageal junction locates at C5–6 intervertebral space and at the inferior border of the cricoid cartilage. The UES consists of the three muscles (cervical esophagus, cricopharyngeus, and inferior pharyngeal constrictor) and the surface of the cricoid cartilage [2]. Its role is to prevent air from entering the digestive tract during inspiration and to protect the airways from aspiration by preventing esophageal contents refluxing into the hypopharynx [3].

The cricopharyngeus is the most important muscle in the sphincter, and it attaches to the dorsolateral aspect of the lower part of the cricoid cartilage, forming a horizontal band, like a c-clamp. The muscle presents unique features for maintaining constant basal tone and for relaxing rapidly when required, including presence of both slow-twitch and fast-twitch muscle fibers, absence of a spindle or median raphe, and a large amount of connective tissue [3]. However, most

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of the high-pressure zone corresponding to the UES is related to the projections of the cricoid cartilage and arytenoid cartilages [3].

Physiology

The cricopharyngeus is innervated by the pharyngeal plexus, which is supplied by three major nerves: vagus nerve branches, including the pharyngeal branch, the glossopharyngeal nerve, and sympathetic nerve fibers from the superior cervical ganglion [4]. Acetylcholine is the principal neurotransmitter for efferent innervation, acting via skeletal muscle nicotinic receptors.

The pressure profile of the UES shows axial asymmetry with a sharp ascent in its upper part and a more gradual decline, as well as marked radial asymmetry [3]. The cricopharyngeus corresponds to the distal part. The resting pressure ranges from 30 to 110 mmHg, but the UES basal tone is lower in full-term neonates as compared to adults, although they present similar deglutitive relaxation [3, 5]. Resting UES tone also varies with head position, phonation (increase), higher pitch notes (increase), and inspiration (increase).

Swallow

During swallow, the continuous spike activity of the cricopharyngeus ceases, due to a transient chloride-dependent inhibition of active lower motor neurons in the brainstem innervating the UES [3]. Anterior motion of the hyoid during its superior excursion, by contraction of the suprahyoid muscle, is also required to abolish the residual pressure and open the sphincter [3]. Next, the relaxed and open UES actively contracts as the deglutitive pharyngeal peristaltic wave reaches the sphincter, reaching twice the resting pressure. The UES opening can be independently modulated by bolus volume and viscosity.

Reflexes

Relaxation follows an abrupt distention of the esophagus, as in belching. The relaxation differs from that associated with swallows as it may be partial and lasts more and the associated hyoid movement exhibits less amplitude [3, 6].

Relaxation of UES also follows most (79%) transient lower esophageal sphincter relaxation (tLESR), but contraction happens in 8% [6]. It may happen before or after the tLESR, and it is more variable in completeness than that observed in swallows. It is generally associated with depressurization of the EB (suggesting air venting) and presents higher median pressure, longer duration, higher incidence of incomplete relaxation, and lower maximal after-contraction amplitude [6].

UES pressure may increase with gagging and slow esophageal distension. It is controversial if acidic content of the bolus enhances UES relaxation [6]. Pharyngeal stimuli, such as infusion of water and air, may also generate UES contraction in adults. On the other hand, in newborns, such stimuli generate pharyngeal swallows rather than UES contraction, possibly as a defense reaction against aspiration [7].

Esophageal Body

The esophagus is a flattened muscular tube that is collapsed between swallows, but can distend to 2 cm in the anterior-posterior dimension and 3 cm laterally to accommodate an ingested bolus [8]. The organ is topographically divided in three parts: cervical, thoracic, and abdominal.

The cervical esophagus extends from the pharyngoesophageal junction to the suprasternal fossa [8]. At this level, the esophagus is bordered anteriorly by the larynx and trachea, posteriorly by the vertebral column, and laterally by the carotid sheaths and the thyroid gland. The thoracic esophagus extends from the level of T1–T10 or T11, lying posterior to the trachea and the pericardium; anterior to the vertebral column and aorta; and sided by the mediastinal pleura [1]. The abdominal esophagus extends from the diaphragmatic hiatus to the cardia, lying in the esophageal groove on the posterior surface of the left lobe of the liver, on the right of the gastric fundus, being posterior to the left vagal trunk and anterior to the diaphragmatic crura and the aorta.

Esophageal arterial supply is segmental, coming mostly from the inferior thyroid artery (UES

and cervical esophagus), esophageal branches of the aorta (thoracic esophagus), the left gastric artery (LES and distal esophagus), and the splenic artery (distal esophagus) [1]. Venous drainage of the proximal two-thirds drains to systemic veins; the distal third drains to the portal system, but there are plenty of connections between the two systems [1]. Proximal third lymphatic vessels drain into the deep cervical lymph nodes, while middle third lymphatic vessels drain into the superior and posterior mediastinal nodes, and distal third lymphatic vessels follow the left gastric artery to the gastric and celiac lymph nodes [8].

Sensory innervation comes from vagus and spinal nerves. Spinal afferents have their cell bodies in the dorsal root ganglia and terminate in the spinal column and in the nucleus gracilis and cuneatus in the brainstem [9, 10]. Motor innervation is predominantly vagal.

Physiology

Esophageal muscle is phasic, without resting tone. However, some authors have identified a tone that is inhibited during abrupt distention of esophageal lumen and helps preventing reflux episodes [11]. There are intramural inhibitory (nitric oxide) and excitatory (acetylcholine) neurons, which receive inputs from preganglionic neurons located in the dorsal motor nucleus of vagus. Cholinergic excitatory innervation is most marked in the proximal esophagus and decreases gradually in the distal part, while inhibitory (nonadrenergic noncholinergic) increases distally. Vagally activated inhibitory neurons generate the latency of peristalsis.

Primary Peristalsis

Primary peristaltic waves are associated with swallows and can be triggered at will or by reflex. They assist the gravity to propel the bolus through the esophagus and participate in the clearance of reflux episodes [12]. The striated muscle peristalsis depends on sequential activation of motor neurons in the nucleus ambiguous, without any triggering peripheral mechanism [13].

The spread of peristalsis to the smooth muscle depends on coordination of the central and neural peripheral circuitry and myogenic properties. The smooth muscle segment presents cholinergic (excitatory) and nonadrenergic noncholinergic (inhibitory) effector neurons. Also, muscle cells interact and operate as a functional unit, while the interstitial cells of Cajal modulate the muscle nerve interaction [14]. There is a latency period between the onset of a swallow and contraction of esophageal circular smooth muscle. Early in this period, intramural neurons release nitric oxide that causes initial hyperpolarization and inhibition of esophageal muscle. Latency duration increases from proximal to distal esophagus, and this gradient is the basis for esophageal peristalsis [15].

Esophageal contractions are limited by two inhibitory phenomena: initial inhibition and refractoriness [16]. Initial inhibition is the inhibition of any activity in the esophagus that may be occurring at the time of vagal stimulation, and its degree increases with increasing frequency of stimulation. Refractoriness is the inhibition of any evoked contraction that may tend to occur during and soon after the ongoing esophageal response to a previous stimulus. As a consequence, repetitive swallowing at short intervals produces an esophageal response characterized by quiescence until the last of the swallows, which is then followed by an esophageal contraction [16].

Primary peristalsis has been observed in the fetus as early as 32 weeks of post-menstrual age (PMA) [17]. The mean maximum peristaltic wave amplitude increases from 33 to 39 PMA in the proximal esophagus, both in primary and secondary peristalsis, but not in the distal esophagus [18]. Newborns present lower amplitude, slower velocity of propagation, and greater duration of the contraction than adults [5]. The amplitude of peristaltic wave in the distal esophagus was found to increase with age, peaking in the 50s [19]. Elderly patients frequently present abnormal esophageal contractions, possibly due to reduction in the number of ganglion cells with age and inflammation of Auerbach's plexus [20].

Secondary Peristalsis

Secondary peristalsis is a response to esophageal distension triggered by afferent and efferent

innervation through vagus. The secondary peristalsis depends on peripheral mechanisms and also involves inhibition followed by excitation. It is uncertain if the chemical content of the bolus (acidic or not) influences the threshold to initiate the peristalsis [11]. The secondary peristalsis is a clearance mechanism, after primary peristalsis and reflux episodes [11]. The mean maximum peristaltic waveform amplitude is lower in the distal esophagus but not in the proximal [18].

Clearance mechanisms are present in preterm infants, and they present similar latency period to trigger them and similar volume-dependent increase in the UES pressure following infusion of liquid in the esophageal lumen [21]. The presence of secondary peristalsis has been observed in the fetus as early as 32 weeks of post-menstrual age [17]. On the other hand, preterm babies (33 weeks) present lower volume threshold for mechano- and chemostimulation to evoke secondary peristalsis [21]. In response to acidic content, the main clearance mechanism is primary peristalsis in 33-week infants, but secondary peristalsis in 36-week infants [21].

Lower Esophageal Sphincter (LES)

The gastroesophageal junction is a dynamic structure composed by the LES, the crural diaphragm, and components of the gastric muscle (Fig. 4.1) [12]. Its function is to avoid gastroesophageal reflux, without impair swallowing and appropriate reflux of gaseous contents. There is a thickening of the esophageal circular muscle layer in the LES, which may be located above, at the level or below the esophageal hiatus. This thickened region is limited by a fascia, forming a discrete muscular ring [22]. Crura circle the proximal 2–4 cm of the LES and determine inspiratory spikelike increases in LES pressure as measured by esophageal manometry [23].

Resting

Resting tone is believed to be predominantly due to intrinsic muscle activity because the resting LES tone persists even after surgical or pharmacologic destruction of all neural input [24]. LES muscle fibers present unique features, as differentiated composition of contractile proteins and continuous electrical spike activity, that play a role in keeping the tone by myogenic properties [13]. Also the diaphragmatic crura contribute to the LES pressure, contracting during inspiratory effort [25].

Motor innervation depends on vagus, which provides both excitatory (cholinergic) and inhibitory (nitrergic) innervations to the LES, but they influence the resting tone only when stimulated. Neurohormones modulate basal LES tone (figure) [12, 13].

In preterm babies younger than 29 weeks PMA, LES presents lower basal pressure (3.8–5 mmHg) as compared to full-term infants (18.1–23 mmHg) [12, 26].

Reflexes

Excitatory stimuli from vagus are related to acetylcholine and substance P neurotransmitter, while the inhibitory stimuli depend mainly on nitric oxide [13]. Deglutitive transient LES relaxation (dTLESR) begins within less than 2 s of a swallow and is mediated by vagal inhibitory pathway and the postganglionic myenteric neurons that act by releasing nitric oxide [13]. The relaxation usually lasts 8–10 s and is followed by a contraction, continuation of esophageal peristalsis, in the proximal part of the LES that lasts 7–10 s.

Pharyngeal tactile stimuli elicit LES contraction through a reflex that follows the same pathway and can be abolished by bilateral vagal nerve section or cooling. Esophageal distention by a bolus of liquid or food triggers relaxation of the LES through motor fibers originating in the dorsal motor nucleus of the vagus and the compact portion of the nucleus ambiguous when the distention happens in the striated part of the esophagus [12]. On the other hand, distention in the smooth muscle zone seems to result in a reflex relaxation from intramural neurons [27].

tLESR is not associated with swallowing, and it helps to regulate gastric distension, by allowing belching and vomiting. tLESRs are a vagovagal reflex that involves only the inhibitory pathway [13]. Sensory fibers from infradiaphragmatic receptors, such as fundic mechanoreceptors, ter-

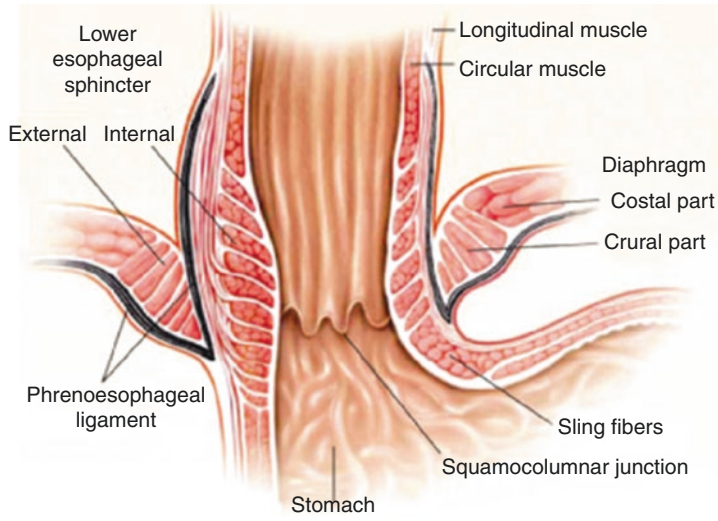

Fig. 4.1 Anatomy of the esophagogastric junction (Adapted from GI Motility online (May 2006) | doi:10.1038/gimo14)

REDUCE LES PRESSURE
- Nicotine
- Beta adrenergic antagonists
- Cholecystokinin
- Secretin
- Vasoactive intestinal polypeptide (VIP)
- Calcitonin gene-related peptide
- Adenosine
- Prostaglandin E
- Nitric oxide donors (i.e nitrate)
- Glucagon
- Atropine
- Gastric inhibitory peptide
- Calcium channel blockers
- Morphine
- Inhibitors of phosphodiesterase-5
- Decreased ventilatory drive (apnea)

INCREASE LES PRESSURE
- M2 and M3 receptor agonists
- Alfa adrenergic agonists
- Motilin
- Pancreatic polypeptide
- Bombesin
- Angiotensin II
- Metoclopramide
- Cisapride
- Gastrin
- Substance P
- Prostaglandin F2alpha
- Hypoxia

minate in the caudal brainstem (nucleus tractus solitarius), from which downstream motor nuclei such as the dorsal motor nucleus of the vagus and nucleus ambiguus are activated. These nuclei then send afferent input to the LES, esophageal wall, pharynx, and crural diaphragm and activate tLESRs [12]. tLESR combines cessation of tonic cholinergic excitation and active inhibition of muscle contraction through nonadrenergic noncholinergic pathways [12]. The most important noncholinergic, nonadrenergic mediators involved are NO and VIP [12]. Deep inspiration may also trigger tLESR [12]. Different from dLESR, tLESR is associated with concurrent inhibition of diaphragmatic crural activity. Also, the relaxation is longer (more than 10 s) and more variable, ending with an unpredictable pattern of terminating motor event in the esophagus, either primary peristalsis or spontaneous contractions, which seems to be more frequent [28]. tLESR triggering is enhanced by phosphodiesterase-5 inhibitors and inhibited by GABA-B agonists. Finally, cholecystokinin (CCK) receptors may play a role, and CCK released on food entering the duodenum may enhance tLESRs triggering [29].

Tests to Detect Esophageal Contraction Abnormalities

Indications

Esophageal manometry is considered the gold standard for assessing esophageal motor activity, especially diagnosing nonstructural dysphagia [30]. Both normal and abnormal esophageal

contractions and bolus movement can be detected without the use of radiation [31]. However, the diagnostic tool should be used only after a careful history and endoscopic and fluoroscopic examinations have ruled out any organic pathology or cardiopulmonary involvement [30]. Following these considerations, esophageal manometry can successfully evaluate upper and lower esophageal sphincter (UES and LES) pressure, esophageal body contraction amplitude, and peristaltic sequence [32, 33]. Causes of unexplained or noncardiac chest pain, systemic collagenosis, and symptoms related to gastroesophageal reflux disease (GERD) [30, 32] may also be identified. Although esophageal manometry does not diagnose GERD, it may be used to evaluate a patient prior to antireflux surgery [30, 34] to rule out scleroderma esophagus and achalasia and to adequately access esophageal length [32].

However, both standard manometry and HRM are not definitive diagnostics when it comes to achalasia. Both tests fail to detect brief periods of EGJ relaxation, which affects peristalsis and pressure within the distal esophagus. While this data has not yet been fully refined, it may prove significant to accurate achalasia diagnosis. HRM may prove beneficial in subclassifying achalasia into classic, spastic, and combined with esophageal compression [35].

Esophageal manometry is contraindicated in cases of pharyngeal or upper esophageal obstructions, severe coagulopathy, cardiac conditions in which the patient is intolerant of vagal stimulation, and patient noncompliance [30].

Methods and Equipments

To ensure an accurate diagnosis, it is necessary to thoroughly understand the many technical issues of esophageal manometry [36], use proper instrumentation [30], and maintain a standard in technique and evaluation among laboratories [32]. Differences in practice, measurement, and interpretation may hinder an accurate diagnosis [32, 37].

Equipment

Two types of solid-state intraluminal microtransducers have replaced the earlier water-infused manometry systems, ensuring accurate qualitative and quantitative esophageal pressure recordings [32, 38]. Unidirectional transducers measure pressures in one direction, while circumferential transducers measure pressures in 360°, and corresponding software automatically averages the results. Standard catheters are now equipped with up to four unidirectional or proximal transducers and one circumferential transducer, each transducer placed 5 cm apart [38]. Measurements are similar when using either a unidirectional or single circumference transducer [38].

Successful manometry requires a three-channel, triple-lumen catheter and a pneumo-hydraulic capillary infusion system with deltaP/deltaT >150–200 mmHg/s [30]. To study the esophageal body and LES, data should be recorded at a rate of ≥8 Hz, noting LES tonic (pressure) and phasic (relaxation) activities in addition to the esophageal body amplitude and peristaltic activity [30].

Evaluations and Recordings

Ideally, the manometry catheter is placed from the pharynx to the stomach, with sensors in and around the sphincters [37]. The catheter is initially placed in the stomach and then rotated in 0.5-cm increments [38]. The study can be successfully completed with the catheter in one position and the patient swallowing 10.5-mL swallows, spaced 20–30 s apart [32]. Systematically evaluating the LES, smooth muscle of the esophagus, and if needed, the proximal esophagus and upper sphincter enables evaluation of LES pressure, length, and residual pressure; distal esophageal body strength and function; and if needed, proximal esophagus and UES studies [32]. All recordings are automatically interpreted by embedded software, but it is important to review the readings independently and provide a written impression [32].

Table 4.1 Normal parameters for esophageal motility studies

	Normal values
Esophageal manometry	Pressures:
Stationary	LES during H_2O swallow [34]: <5 mmHg[a]
24 h	LES resting mid-resp. [38]: 15–45 mmHg
	LES resting length [38]: 2–5 mmHg
Ambulatory	Contraction amplitude at 5 and 10 cm [31]: ≥30 mmHg
	Resting pressures [33][b]:
	UES: 116 ± 9.6 mmHg
	LES: 24.0 ± 2.0 mmHg
	Contraction amplitude [33][b,c]:
	Upper: 60.7 ± 9.5 mmHg
	Lower: 924.0 ± 3.3 mmHg
	Contraction duration [33][b,c]:
	Upper: 2.7 ± 0.2 s
	Lower: 3.5 ± 0.1 s
Stationary	Swallows [33][c]:
Pediatric numbers—because this is one of few studies, not meant to be used as a gold standard/ authors	Upper: 100 %
	Lower: 3.5 ± 0.1 s
	Resting pressures [39][b]:
	UES: 62.5 ± 19.4 mmHg
	LES: 24.0 ± 7.6 mmHg
High resolution	Intraluminal esophageal pressures [39][b]:
	17.6 ± 4.7 mmHg before wet swallows
	↑ 43.1 % ± 47.5 % after swallows
	Per Chicago Classification [40]:
	<3 cm defect in 30-mmHg isobaric contour
	IBP <15 mmHg
	DCI <5,000 mmHg s^{-1} cm^{-1}

GEJ gastroesophageal junction
[a]Values are often lower in the sitting than supine position
[b]Values presented as mean ± SD
[c]Upper, lower refers to location in the esophagus
[d]Measured from cricopharyngeal sphincter to the GEJ [41]

Normal Values

For accurate recordings, pressure data are obtained from at least three sites, each spaced 5 cm apart. The most distal pressure transducer should be located no more than 3 cm distal to the pH sensor. Data are recorded on an electronic data logger and analyzed by software. Manual tracings of pressure and pH will help locate abnormal readings and correlate them to pain periods. A normal LES reading relaxes below 5 mmHg during water swallowing [34]. Normal values for esophageal motility testing are provided in the Table 4.1.

Esophageal motor functions vary throughout the day, with more activity noted during meals, as propulsion forces solids down the esophagus, creating longer, higher amplitude contractions [33, 42]. Values are often lower in the sitting than supine position, possibly because intra-abdominal pressure during sitting increases intrinsic muscle tone [38]. There may also be a

connection between esophageal motor activity in the supine position and rapid eye movement during sleep [33]. The normal mid-respiratory LES resting pressure has been noted at 15–45 mmHg, and the corresponding normal LES resting length is 2–5 mmHg [38]. Values may also be affected by age and gender. A study of adults by van Herwaarden et al. determined that females have higher resting pressures than males. They also determined that UES resting pressures and UES relaxation interval and rate show an inverse correlation with age, while UES residual pressure increases. This results from a loss of basal tone and a decrease of UES compliance [43].

Stationary Esophageal Manometry

Stationary esophageal manometry, often performed with the patient in the supine position, is used to evaluate the UES and pharynx and to determine the upper margin of the lower esophageal sphincter (LES) prior to ambulatory manometry. Although solid-state manometry is capable of recording in the upright position, normal values for that position have yet to be determined, and the position affords more ineffective contractions [32].

Ambulatory 24-h Esophageal Manometry

Limited studies have been done on normal readings during a 24-h ambulatory esophageal function, and ambulatory studies have been criticized because of the individual variables involved, although the variables may not be different than those of stationary manometry [42]. Ambulatory 24-h esophageal manometry is beneficial to diagnose esophageal spasm because pain symptoms often correlate with abnormal motility or acid reflux, neither of which may be diagnosed during stationary manometry. Using a solid-state combined manometry and pH probe, the probe's pH sensor is positioned 5 cm above the upper margin of the LES. Routine treatments, such as a proton pump inhibitor, are continued during the study [44].

High-Resolution Esophageal Manometry

Conventional manometry details the esophageal pressure profile, but it does not provide information on bolus transit or esophageal emptying [37]. As a result, diagnosis based on manometry is somewhat subjective [37]. Given that there is poor association between conventional manometry and symptoms, high-resolution esophageal manometry (HRM) is a natural evolution [44, 45]. Technical advances have led to the development of powerful computerized acquisition systems, high-fidelity multichannel perfusion pumps, and manometric catheters, thereby enabling a higher resolution of measurements [39]. Pressure data are then transformed into a topographic colored data sheet of continuous esophageal pressure [37, 39, 45].

Algorithms expand the data into pressure topography plots, which characterize the spatial limits, vigor, and integrity of contractile segments along the esophagus in addition to distinguishing between pressure and contractions. Studying 400 patients and 75 controls, Kahrilas et al. formulated the Chicago Classification system to reclassify esophageal motility to coincide with the new colored plots. This system essentially refines diagnosis and essentially eliminates nonspecific esophageal motor disorder [40] because all manometry findings are nonspecific, and there is always more than one diagnosis associated with each noted pattern. Since its development, the Chicago system has been subtly modified by research groups around the world, and most likely, the system will continue to evolve for many years [35].

The HRM catheter can be positioned to record pressures just above the UES and also below the LES, thereby recording normal esophageal motor function in addition to dysfunction [39]. Pressure sensors on the HRM catheters are spaced 1–2 cm apart, rather than 5 cm as in conventional or solid-state manometry, and HRM catheters may have as many as 36 sensors [35, 39, 44]. Multiple sensors eliminate movement-related artifact [35, 40] and the dependency on correct sensor positioning [37], both problems with conventional manometry.

While unidirectional and circumferential HRM catheters are available, they do not appear to provide significant benefit [37].

While the correlation between conventional manometry and HRM is high, HRM offers numerous advantages:

- Presents pressure data in pattern recognition and real time, allowing objective measures and standardized interpretation [35, 37]
- Provides intuitive and easy to learn technology, offering reproducible studies [35, 37]
- Allows quicker and easier high-quality studies, without need for catheter pull-through and sensor positioning [35]
- Reveals complex functional anatomy of esophageal peristalsis and esophagogastric junction, thereby improving ability to predict success or failure of bolus movement through esophagus [37, 44, 45]
- Detects reflux events and distinguishes components of antireflux barrier, allowing study of their interaction [44]
- Increases diagnostic accuracy of achalasia and its subclassifications, functional dysphagia, and esophageal spasm [37, 44]
- Defines, with combined impedance, intraluminal pressure gradients within the esophagus and across sphincters [45]

HRM is useful in pediatrics and allows the clinician to differentiate between aperistalses due to ineffective motility or due to achalasia [46]. Recommendations for HRM in pediatrics include [46]:

- Avoid sedation, if at all possible.
- Identify LES using standard manometry.
- Run baseline of LES pressure once patient is relaxed.
- Aim for maximum tolerated volume in ten wet swallows: 5 mL if >5 years, 2 mL <5 years, and 0.5–1.0 mL for infants.
- Study solid swallows if patient has symptoms following solid food.

Despite the advantages of HRM, there is the basic issue of how to apply the advanced technology to evaluate patients. Most likely, a new language may need to be developed [35, 45]. There are limitations to this new technology, and studies are needed on cost-effectiveness compared to conventional manometry and on the benefit of HRM in all applications [44]. While HRM indirectly estimates bolus transit, it can determine and localize bolus transit failure [37]. Accurate readings require a skilled clinician who has been trained in manometric recordings and interpretations. The clinician should also be cautioned against misinterpretation, which could lead to unnecessary or ineffective treatment [44]. In addition, current classification of esophageal motility, developed for conventional manometry, may need to be reconsidered [35].

High-Resolution Impedance

Intraluminal impedance provides information on bolus transit and avoids the radiation exposure of fluoroscopy. Combined manometry and impedance provide information on both bolus transit and motor function, thereby allowing tighter categorization of esophageal dysfunction and treatment. Combined HRM and impedance take accurate diagnosis one step further by refining the diagnosis and management of achalasia, functional obstruction, and rumination. Together, they also distinguish pressure values for abnormal bolus transit [37].

Impedance detects the type of acid (liquid, gas, or mixed) and the proximal extent of reflux, regardless of its acidity. However, the ability to detect small amounts of reflux have yet to be determined, suggesting that combined impedance and pH monitoring may be required to fully evaluated reflux [45].

High-Definition HRM

Technologies will continue to evolve, and high-definition HRM catheters, with more pressure sensors, closer together, are being developed. This newer development will offer enhanced spatial resolution and radial pressure detail, thereby allowing detailed study of the CD component of EGJ pressure and the intragastric component of EGJ [45].

Tests to Evaluate Esophageal Bolus Transit and Clearance

Videocineroentgenography

Videocineroentgenography, also known as videofluorography (VFG) [47], provides a highly sensitive morphodynamic study of swallowing, including vocal cord and soft palate motility, oral and pharyngeal phases of swallowing, and pooling of contrast agent in the sinuses, and is a valid study of the overall esophagus [47]. The test helps identify esophageal motor alterations, such as clearing deficit and dilatation, GERD, and hiatus hernia, and may be successfully used as an indicator of the progression of systemic sclerosis [47]. Early stages of esophagitis, however, must be identified by endoscopy [47].

Initially, the pharyngeal function is dynamically evaluated by recording the ingestion of barium. Barium is ingested voluntarily, but it may also be instilled with a syringe into the cheek pouch [48]. Possible abnormalities include abnormal tongue movement, pharyngeal muscle dysfunction, laryngeal penetration, and aspiration [49]. Then, high-density barium is swallowed in upright position in order to coat the mucosa with a thin layer of contrast, for double-contrast frames, which are useful to evaluate the esophageal mucosa [50]. Next, low-density barium is ingested in the prone position (right anterior oblique position) to evaluate esophageal motility. Five swallows with at least 20-s interval are required in this part [50]. Finally, more low-density barium is ingested to distend the lumen and detect strictures [49]. Children need to be immobilized, and the use of an Octostop device (Octostop, Laval, Quebec, Canada) or special car seat is beneficial for children under 3 years and may reduce a child's fear [48]. Barium, which is generally instilled during voluntary swallowing, can be made more palatable with flavoring packets or mixed in milk [48]. Timed barium esophagogram follows a different protocol to evaluate the esophageal emptying, with three radiograph exposures (1, 2, and 5 min) after ingestion of 250 mL of low-density barium [51].

Abnormal motility is defined by abnormal peristalsis observed in two or more discrete swallows [49]. Achalasia features a flaccid and dilated esophagus, with a beak-like narrowing at the gastroesophageal junction. Diffuse esophageal spasm is characterized by intermittently absent peristalsis with lumen obliterating nonperistaltic contractions, producing a typical corkscrew appearance [49]. Finally, double-contrast examination may suggest diagnosis of esophagitis (peptic, infectious, and eosinophilic) and strictures.

Although radiology cannot provide a definitive diagnosis, it is a useful screening test in patients with dysphagia, as it may suggest motility abnormalities and rule out strictures. Overall, radiology is 80 % sensitive and 79–95 % specific for diagnosing esophageal motility disorders [50, 52]. The sensitivity of the study depends on the number of swallowing studies performed in both the upright and supine positions. A higher sensitivity may be noted with the patient in the prone position, although more abnormal contractions are detected in the upright position. The reason for this remains unclear [52].

A major disadvantage of the method is the exposure to radiation, which can be diminished by optimizing the X-ray beam and using beam filtration, additional layers of aluminum and copper filtration, low-dose pulsed fluoroscopy, minimized fluoroscopy time, and tight collimation [48]. Also, the total number of higher dose spot film-type exposures can be reduced by using fluoroscopy capture technology or frame grab. The use of analog or digital recording may allow for recording of a limited number of swallows.

Esophageal Transit Scintigraphy

Esophageal scintigraphy allows evaluating the esophageal emptying, the bolus transit through its segments, and the presence of reflux in all evaluated segments [53].

After ingesting radiolabeled bolus, images are acquired at four to ten frames per second for 60 s (or 0.5 s for 40 s) [54]. The test is performed with a large field gamma-camera that views the entire

organ. Anterior and posterior views can be used, being anterior preferred when oral and pharyngeal phases are being evaluated and posterior preferred when the interest rely on the esophagus. The Exam can be performed with ^{99m}Tc-sulfur colloid, ^{99m}Tc-nanocolloid, ^{99m}Tc-diethylenetriaminepentaacetic acid (DTPA), or any other nonabsorbed radiopharmaceutical, mixed with water or juice. The minimum dose is 7–11 MBq. A semisolid bolus may be used but it is not as standardized as liquid bolus [53]. Although an upright position is more physiological, the supine position is better to evaluate clearance as this position removes the effect of gravity.

The clearance is indicated by retained radioactivity in the esophagus. In adults, the mean residual radioactivity at 20 s is 6.4 ± 1.8 %, and values over 10 % (mean + 2 standard deviations) are abnormal [54]. Based on one wet swallow (15 mL, 11 mBq) and three successive dry swallows (5 s interval), a fraction >19.8 % in the posterior view (or 13.1 % in the anterior) at the fourth swallow is considered abnormal in the supine position [55].

Scintigraphy may suggest motility abnormalities, such as achalasia, by detecting delayed esophageal emptying with 91 % sensitivity and 98 % sensitivity [53]. Also, it can be used to evaluate the esophageal function after endoscopic treatment of achalasia [56]. Advantages of the method include the compression of the exam to a single image and the better accuracy to evaluate emptying rate as compared to conventional radiology. Its interpretation relies on objective and quantifiable measures, depending less on the interpreter [54]. On the other hand, it requires equipment not widely available and does not evaluate the esophageal anatomy well. Also, the test is not properly standardized, and protocols vary significantly between centers.

Impedance and Ambulatory Esophageal Impedance and pH Monitoring

Impedance is the resistance to electrical flow in an electric alternating current (AC) circuit. In this test, an AC is passed between electrodes, and each pair of two electrodes forms an impedance channel between them. The baseline impedance is a measure of impedance in the esophageal mucosa, as the lumen is collapsed and the mucosa is in contact with the electrodes. Although there is no normal value for baseline, it is lower in inflamed mucosa, in the proximal esophagus, in Barrett's esophagus, and in dilated esophageal lumen and when liquid stasis is present [57]. Changes in the impedance reading are related to the passage of substances presenting impedance that is different from the esophageal mucosa: a liquid bolus diminishes the impedance (presenting lower resistance to the electrical current); and a gaseous bolus increases the impedance (more resistance). At the distal end of the catheter is placed a pH sensor that allows determining the chemical content of the bolus. Combined ambulatory esophageal impedance and pH monitoring allows evaluating not only the bolus transit and clearance but also the clearance of refluxate bolus and the chemical clearance of the esophageal lumen after a reflux episode.

The exam employs a polyvinyl catheter (2.13-mm diameter) with six impedance sensors and a distal pH probe that is located to 13 % the distance between LES and the nostrils. Specific catheters are available for infants, children, and adults.

The impedance test for esophageal transit time is performed with a protocol similar to that of esophageal manometry, with ten discrete liquid swallows and ten discrete viscous swallows. Bolus entry in a channel is defined by a drop of 50 % of baseline and exit by return to that point. Impedance has been validated, with a 97 % concordance with fluoroscopy in detecting normal bolus transit [58]. Total transit time is the interval elapsed between entry in the first channel and exit in the last distal channel. Frequently a small amount of air is observed in front of the bolus. This leads to a brief increase in the impedence that is not accounted for in the bolus transit. The standard impedance criteria for determining transit passage do not predict reliably bolus transit in the hypopharynx, the UES, and the proximal esophagus. Szczesniak et al. (2008) proposed different

cutoffs for impedance in these locations [59]. According to them, a drop to 71% of baseline would define bolus entry in hypopharynx, 72% in UES, and 80% in proximal esophagus, while clearance could be defined by 0% recovery (nadir) in the hypopharynx, 5% in UES, and 19% in the proximal esophagus. With these criteria, the agreement between fluoroscopy and impedance would improve, but would still remain fair to moderate, because impedance is not good at evaluating bolus transit before esophagus, because pharynx is not a collapsed organ [59].

The main parameter evaluated is the proportion of swallows that present complete bolus transit. Complete bolus transit is achieved in 93% of normal individuals for at least 80% liquid swallows and 70% viscous swallows [60–62]. An abnormal bolus transit can signify stasis, if there is a fail in demonstrating bolus exit or if the impedance falls after transient recovery, or retrograde escape, defined by the return of the bolus to an area previously cleared [58]. This last event happens generally after a new swallow before 30 s.

The bolus velocity, bolus transit time, chemical clearance, and distal baseline after liquid and viscous swallows can also be evaluated. Bolus velocity is slower for viscous bolus (2.56 cm/s± 0.24) than for liquid bolus (water, 3.81 cm/s±0.31) [63]. Distal impedance after liquid swallow and after viscous swallow is abnormally low in patients with scleroderma, achalasia, and ineffective esophageal motility compared to healthy volunteers and normal patients [57].

Impedance as a test for evaluating bolus transit is mainly indicated in patients with nonobstructive dysphagia and before an antireflux surgery. Impedance cannot replace fluoroscopy, because it cannot evaluate swallows of solid bolus. Also, it does not provide any information on the anatomy of the organ, although it does provide useful information on mucosal integrity [64]. Impedance is the only test that evaluates bolus transit without radioactivity exposure, making it suitable for pregnant women and children, as well as repeated tests are needed. However, the impedance is not useful for diagnosing achalasia. In these patients, a low baseline may be found, due to stasis and inflammation. Also, air trapping makes the exam technically difficult [65]. The exam has not been tested in the follow-up of these patients posttreatment.

Prolonged combined impedance-pH monitoring is useful in evaluating gastroesophageal reflux, mainly when atypical symptoms are thought to be related to reflux episodes. The test is better than prolonged pH monitoring in finding a significative symptom association with reflux episodes. Also, it is useful to evaluate GERD refractory to therapy [64]. Esophageal impedance monitoring with simultaneous gastric pressure evaluation identifies patients with rumination better than esophageal pH monitoring, as rumination generally involves nonacid bolus. Gastric manometry demonstrates increase in the intragastric pressure that initiate the event, and impedance identifies the consequent reflux event. Finally, supragastric belching can also be identified through impedance, as it shows air rapidly entering and being expelled in the oral direction, different from gastric belching, when it is possible to observe the oral direction of the air [66].

Esophageal Function Testing

Esophageal function testing (EFT) combines esophageal manometry and multichannel intraluminal impedance monitoring, using a specific catheter with solid-state pressure transducers in the center of impedance channels and a distal pressure transducer. Then, the catheter is passed into the stomach through the nostrils. Intragastric pressure is set as baseline pressure [67]. Next, the LES is identified using the pull-through technique, and the last distal pressure transducer is located at it. In order to evaluate peristalsis and bolus clearance, the patient receives in supine position ten liquid and ten viscous discrete swallows, 5 mL each, 20–30 s apart [60]. Swallows initiated within 10–15 s of a primary swallow are excluded from analysis.

There are three different catheters. A catheter with 11 impedance channels (2 cm each, 2.5-mm diameter) and 4 manometric channels (6 cm

apart) disposed between impedance channels 1 and 2 (proximal to distal), 4 and 5, 7 and 8, and 10 and 11. Another one contains four impedance channels (5 cm each), with one pressure transducer in the middle of each channel (10, 15, 20, and 25 cm from the tip) and a distal pressure transducer located 5 cm from the tip. Recently, a high-resolution catheter is available with 36 pressure sensors (1 cm apart) and 12 impedance channels (2 cm apart, except for a 4-cm gap in the proximal segment) [68].

Esophageal function testing provides information previously obtained in esophageal manometry and fluoroscopy in only one exam. It allows monitoring bolus transit patterns, estimating bolus transit parameters and monitoring swallow associated events (aerophagia, air trapping) [69]. It is indicated for evaluating nonobstructive dysphagia, unexplained chest pain, suspicion of generalized gastrointestinal motility disorder, and preoperative evaluation before antireflux surgery [62]. Its use for primary diagnosis is generally made after endoscopy and fluoroscopy yielding negative. It may be useful to assess longitudinal change and therapeutic interventions. After fundoplication, the EFT is useful in evaluating dysphagia, and incomplete bolus transit is more common in symptomatic patients and in patients with abnormal anatomy after the surgery [70].

Esophageal function testing identifies abnormalities in patients with nonobstructive dysphagia in which manometry would have been normal or unspecific, such as in patients with ineffective esophageal motility and distal esophageal spasm [67]. However, there are no data to evaluate the impact of this information in the management. Also, interestingly, in adult patients with distal esophageal spasm, patients presenting with chest pain presented more frequently complete bolus transit, while those presenting with dysphagia, incomplete bolus transit [31]. EFT has no advantage in diagnosing achalasia, although it may be useful in monitoring the treatment. However, in these patients the exam may be technically challenging, due to air and food trapped in the esophageal lumen. In adult patients with worsening dysphagia after fundoplication, preoperative esophageal function testing shows longer liquid bolus transit time [71].

Pediatric experience with esophageal function test has not been published at this time.

Esophageal contractions are said to be normal (contraction amplitude at 5 and 10 cm above LES of at least 30 mmHg and onset velocity in the distal esophagus less than 8 cm/s), simultaneous (onset velocity greater than 8 cm/s or retrograde onset and an amplitude >30 mmHg at 5 and 10 cm above LES), or ineffective (amplitude less than 30 mmHg). Complete bolus transit is bolus exit in all three distal channels, and incomplete bolus transit is defined by absence of bolus exit in any of the channels, and normally at least 80% liquid swallows and 70% viscous swallows are associated with complete bolus transit [67]. Based on the EFT findings, esophageal motility abnormalities can be divided in two groups: abnormal manometry and transit (achalasia, scleroderma, ineffective esophageal motility, and distal esophageal spasm) and abnormal manometry with normal transit (nutcracker esophagus, hypertensive LES, hypotensive LES, and poorly relaxing LES) [60]. In addition, other impedance parameters can be estimated, such as bolus transit time (time between bolus entry in the proximal channel and exit in the distal channel), velocity, and baseline impedance during resting. Normal values for total bolus transit time (time between bolus entry in the proximal channel and bolus exit in the distal channel) have been proposed for adults, as 5.2–11.9 s (percentiles 5th and 95th) for liquid boluses and 5.9–12.4 s to viscous boluses [61]. Normal values for bolus head advance time (time between bolus entry in the proximal channel and bolus entry in the distal channel) also were proposed for adults, being 0.5–5 s for liquid bolus and 2.8–7.4 for viscous bolus, values that correspond to a speed of 3–30 cm/s and 2.02–5.3 cm/s, respectively [72]. The bolus transit is delayed in patients with ineffective esophageal motility and accelerated in patients with nutcracker esophagus [73]. Recently, EFT with high-resolution manometry has been used with impedance, and an isobaric contour break longer than 3 cm in the isobaric contour of 30 mmHg was associated with incomplete bolus transit [68].

Pathophysiologic Aspects of Esophageal Motility

Pharyngoesophageal swallowing disorders occur with a high prevalence of concomitant disease, often neuromuscular in origin. The disorders are often chronic, with alarming, yet nonspecific symptoms [74]. They may severely affect a patient's quality of life, especially newborns and young children who are easily susceptible to poor nutrition and failure to thrive [75]. Although esophageal motility disorders have been recognized for centuries, there is a lack of large population studies. As a result, disorder prevalence and economic impact are not well characterized, and many treatments have not been standardized [74].

Motility disorders of the esophagus can be classified as primary or secondary disorders. In primary disorders—such as achalasia, diffuse esophageal spasm (DES), or nonspecific esophageal motor disorder (NEMD)—only the esophagus is primarily affected. Secondary disorders, such as reflux esophagitis, are primarily systemic diseases due to physical or chemical injury that affect the esophagus [50]. The pathophysiology of the most common esophageal motility disorders is described below.

Cricopharyngeal Achalasia

Etiology and Symptoms

Normal swallowing occurs when the cricopharyngeus muscle, a sphincter of the upper esophagus, relaxes, thereby allowing a bolus of food or drink to pass the UES into the esophagus. Primary cricopharyngeal achalasia occurs when the muscle, normally in a constant state of contraction, fails to fully relax and enable swallowing (Fig. 4.2) [76–78]. Problems with PES opening may be due to pharyngeal weakness, possibly due to systemic or neurologic processes. However, many cases of cricopharyngeal achalasia are idiopathic [78].

It occurs most often in middle-aged or elderly patients, but is rare in newborns [77]. While most cases of achalasia occur in the presence of organic disease, other motor abnormalities are generally absent in cricopharyngeal achalasia. Symptoms include dysphagia, choking, cyanosis, salivation, and nasal reflux during feeding [76, 79].

Diagnosis

It is difficult to diagnosis primary cricopharyngeal achalasia, which is most commonly seen in neonates, and confirmed diagnosis is often delayed and sometimes even overlooked [75, 76]. Despite the fact that many cases of cricopharyngeal achalasia are idiopathic [78], anatomic (tracheoesophageal fistula) and functional (esophagus atresia and GER) obstructions must be identified or ruled out with a chest X-ray, barium swallow, and manometry [76]. Neurologic defects should be ruled out by brain ultrasound or computed tomography [77].

A diagnosis of cricopharyngeal achalasia is confirmed following an esophagoscopy that reveals a slight shelf at the level of the UES [75, 76] or cineradiography with lateral views [77]. Radiography shows a persistent prominence of the muscle and an associated narrowing of the PES throughout the entire swallowing [78]. Botulinum toxin injections into the cricopharyngeus muscle have also been used as a diagnostic test in adults to determine the degree of dysphagia related to the muscle [80]. However, following Botox, some patients may develop an inflamed gastroesophageal junction, making myotomy more difficult [81].

Treatment

Achalasia in the premature infant may be self-resolving and best handled with a feeding or gastrostomy tube. Primary cricopharyngeal achalasia requires further treatment, albeit the options are limited: dilatation of the upper esophagus, surgical myotomy of the cricopharyngeus muscle, or drug therapy. Because the disorder is rare and more studies are needed, the efficacy of these options is uncertain [76, 77].

Dilatation, a safe and effective procedure, is more effective in patients with mild dysphagia [79]. The procedure may need to be repeated several times before healthy swallowing is restored. Cricopharyngeal myotomy is not always effective

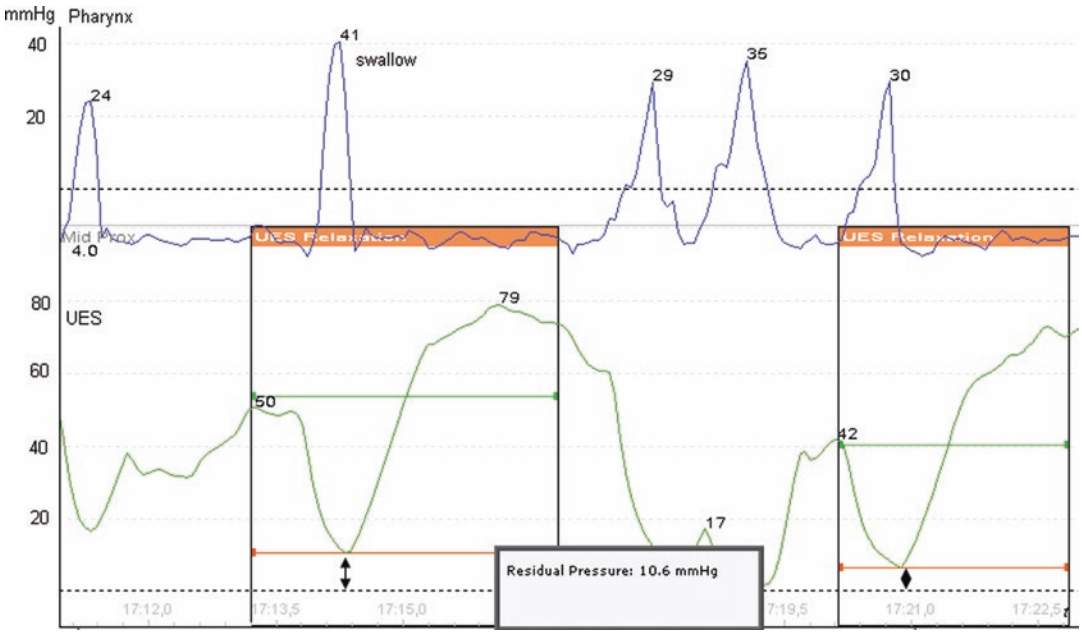

Fig. 4.2 Esophageal manometry in a patient with cricopharyngeal achalasia. Note the swallow followed by incomplete relaxation of UES (*double arrows*), with a resting pressure of 10.6 mmHg. UES: lower esophageal sphincter

and may introduce postoperative complications such as infection and recurrent laryngeal nerve damage. Given the potential complications, some feel that this option should be reserved for patients with residual dysphagia following nonsurgical treatment [75, 76] or patients without other esophageal abnormalities or associated diseases [77]. However, others argue that surgical correction with a complete myotomy provides immediate resolution or a noticeable decrease in symptoms [79]. Myotomy success in reducing the PES narrowing can be measured by a videofluorographic swallow study [78].

Early intervention allows the patient to learn how to swallow during the appropriate development stage [79]. Drug therapy with nifedipine and nitrates may also be beneficial in reducing the muscle tone of the esophageal smooth muscle [77]. But data on their benefits remains scarce, and side effects, such as hypotension, headache, or flushing, have been noted [77]. Injections of botulinum toxin into the cricopharyngeal muscle have been effective in the diagnosis and therapy of adults [80], although it has noted side effects and has yet to be tried in children [76].

Achalasia

Etiology and Symptoms

Achalasia, a rare condition in children, occurs when the LES fails to relax properly, resulting in progressive aperistalsis in the distal two-thirds of the esophagus body (Fig. 4.3). Consequently, the esophagus fails to empty, and material accumulates until enough pressure accumulates and the bolus passes [74]. Although the cause is unknown, most likely, smooth muscle denervation plays a significant role [65, 82, 83]. A primary inflammatory process may be involved, supporting the theory that achalasia is immune mediated [84]. Achalasia is also strongly associated with Chagas' disease, which is caused by the homoflagellate protozoan *Trypanosoma cruzi* and tends to occur in the young [83, 85]. The disorder may be progressive, causing pronounced morbidity [83]. Achalasia may also be associated with the Allgrove syndrome (alacrima, achalasia, and adrenocorticoid deficiency) [86].

Older children with achalasia often have progressive dysphagia to solids and liquids that lasts from several months to several years [65, 82]. Other symptoms include regurgitation (most

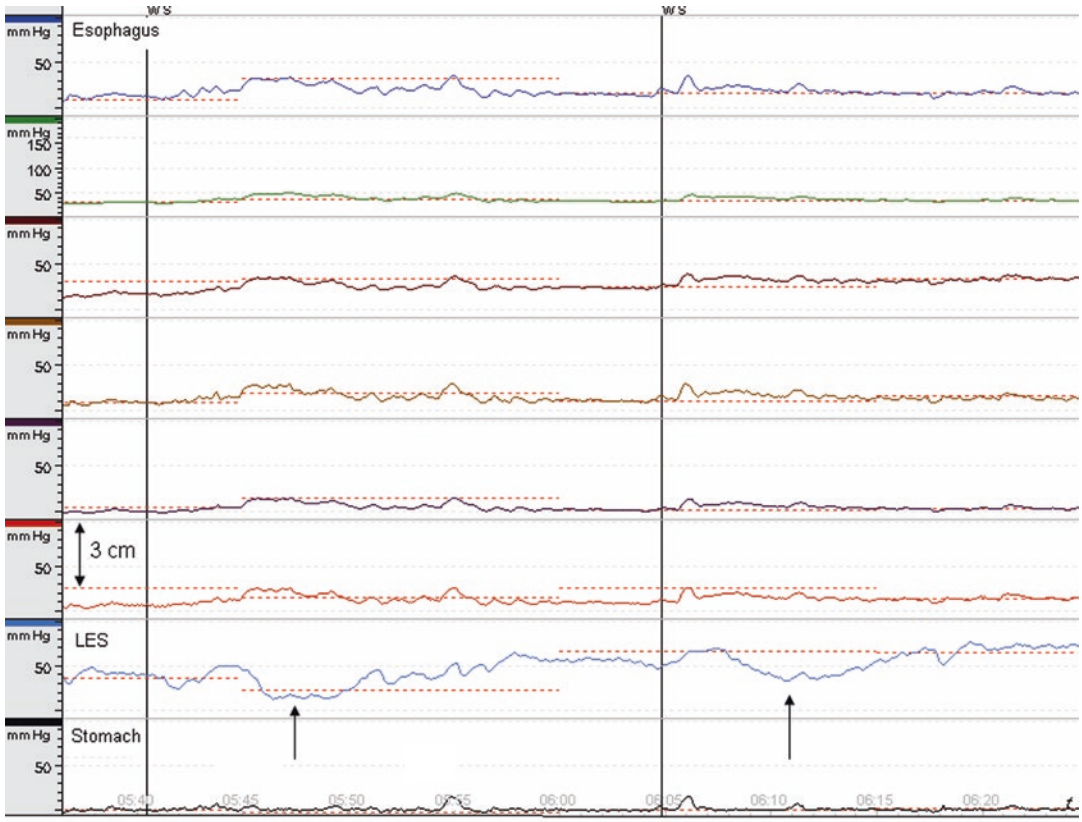

Fig. 4.3 Esophageal manometry in a patient with achalasia. Note the incomplete relaxation of LES (*arrows*) and the absence of primary peristalsis. *WS* wet swallows, *LES* lower esophageal sphincter

often in supine position) [65, 86, 87], chest pain, heartburn often due to stasis of food [88], weight loss [74], coughing (mainly nocturnal), vomiting in children under 5 years of age, and recurrent pneumonia secondary to aspiration [82].

More than one-quarter of children with achalasia may have coexisting conditions including asthma [82]. Pseudoachalasia, which is caused by a tumor at the esophagogastric junction, mimics classic achalasia. Diagnosis is dependent on a surgical biopsy [82]. Patients with achalasia are at increased risk for developing squamous carcinoma [83] and adenocarcinoma and should be followed with routine endoscopy following treatment [87].

Achalasia Subtypes

A study by Pandolfino et al. suggests that there are three subtypes of achalasia, as determined by high-resolution manometry (HRM) [37, 89]:

- Type I or classic achalasia is characterized by a high percentage of failed peristalsis. Patients in this group respond best to Heller myotomy.
- Type II achalasia, which comprises many females, is characterized by pan-esophageal pressurization. Patients in this category respond well to most interventions (Botox, pneumatic dilation, or Heller myotomy).
- Type III patients often have a negative treatment response. Patients in this group have a higher percentage of spastic contraction and chest pain.

Types I and II may represent the natural disease progress, while type III, noted for esophageal spasm, may represent a variant of the disorder. Classifying patients into these subtypes may well determine treatment efficacy [89].

Diagnosis

Prior to diagnosis, it is important to rule out any neurologic involvement in addition to other pathologies or obstructions with an upper endoscopy [82, 87, 90]. Achalasia is most often diagnosed by barium esophagogram, which evaluates both morphology and caliber of the esophagogastric channel [91], thereby identifying the typical "bird beak" or narrowing at the gastroesophageal junction [87, 92]. The esophagus becomes very dilated and tortuous as the disease evolves [92]. However, in the early stages of the disease, the esophagus may have a normal diameter, and a barium esophagogram may not show any abnormalities [51]. Another diagnostic, timed barium esophagogram, provides more dynamic information on esophageal emptying and may objectively assess patient response to pneumatic dilatation and surgery [51].

Although some researchers feel that esophageal manometry may not be necessary if radiographic findings decidedly indicate a diagnosis of achalasia [51], others feel that manometry is the gold standard [87, 90], especially high-resolution manometry (HRM) [93]. HRM is over 98 % sensitive in detecting achalasia compared to conventional manometry, with a sensitivity of 52 % [93]. HRM allows better evaluation of esophageal motor function, including spatial and temporal characteristics, and disordered motor function. This enables an indirect assessment of intestinal wall movements and transit of food contents [39]. Most patients with achalasia also experience more esophageal shortening upon swallowing compared with healthy subjects, although it is unclear if this shortening alters intraesophageal volume [39].

When combined multichannel intraluminal impedance and esophageal manometry (MII-EM) is used as a diagnostic tool, patients with achalasia present with low MII values, which identifies chronic fluid retention, low baseline impedance, elevated intraesophageal and LES residual pressure, and normal [90] or elevated LES pressure [82, 87, 88]. A diagnosis of achalasia can be confirmed by HRM showing aperistalsis of the smooth esophageal muscle and poor or incomplete relaxation of the LES during swallowing. Failed peristalsis is represented on the data scans by a vertical band of color extending from the UES to the LES [39].

Results of esophageal transit scintigraphy correlate with LES pressure and achalasia symptom score, and some researchers use the barium esophagography and scintigraphy to confirm achalasia diagnosis. Scintigraphy can be used to evaluate esophageal emptying and to measure the efficacy of treatment [91].

In one study, functional magnetic resonance imaging (fMRI) was used with success to diagnose achalasia (Table 4.2). The disease morpho-functional alterations were identified and in agreement with findings of conventional videofluoroscopy [41]. fMRI is fast, easy to reproduce, and noninvasive. It also provides images in different spatial planes, the possibility of targeting contrast material, and the elimination of ionizing radiation. There are also disadvantages: low spatial resolution renders study of wall profile more difficult, a temporal resolution below those obtained by radiology, and a restriction to the clinostatic position [41].

Treatment

Because normal motor function cannot be restored, treatments are considered palliative [82] and are aimed at improving LES relaxation and reducing LES pressure [88, 93]. Current treatments comprise medical therapy, endoscopic therapy, and surgery [74], although minimally invasive surgery is now the treatment of choice [81]. Pharmaceuticals, such as calcium channel blockers, nitrates, and botulinum toxin injections, have been used in adults with limited benefits and are eventually replaced with other therapies [74, 81]. Calcium channel blockers and Botox have been used infrequently in the pediatric population [82], and the SSAT Patient Care Committee recommends using Botox only for patients who are poor surgical or dilation candidates [83, 87].

Pneumatic dilation, which reduces the pressure by tearing the muscle fibers and weakening the LES, is routinely used in adults, but carries the risk of perforation [74]. The procedure is the initial treatment preferred to myotomy [91], even though it has a success rate of 70–80 % [88].

Table 4.2 Diagnostic criteria for esophageal dysmotility (values)

Esophageal dysmotility	Diagnostic tests	Diagnostic criteria
Cricopharyngeal achalasia	Esophageal manometry stationary/24-h ambulatory	R/O obstruction [76]
Achalasia	Esophageal manometry with impedance monitoring [82, 87]	Chronic fluid retention
		Baseline impedance ↓
		Intraesophageal pressure ↑
		LES residual pressure ↑
		LES pressure ↑ or normal
		Abnormal bolus transit [37]
		Impaired EGJ relaxation [45]
	HRM	Pressures [39]:
		UES normal or ↑
		LES resting ↑
		Max. esophageal pressures [39]:
		Normal before wet swallows
		↑ Significantly after
		During multiple rapid swallows [46]:
		Aperistalsis
		Lack of EGJ relaxation
		Chicago Classification of classic achalasia [40]:
		Aperistalsis
		Mean IRP ≥15 mmHg
		Colored data [39]:
		Failed peristalsis: vertical band of color from UES to LES
		Failed LES resting: little change in color
	Functional MRI [41]	Morphological findings:
		Narrowing of distal esophagus (>10 mm)
		Dilation of segments above
		Poor relaxation of EGJ
		Inefficient peristalsis
		↑ Bolus transit time to 20
		Advanced disease:
		Marked distension to 60 mm
		Tertiary peristalsis
		Failure to empty organ
	Barium esophagogram	Esophagus appearance:
		"Bird beak" narrowing at GEJ [51, 87, 88]
		Flaccid and dilated above junction [94]
		Early disease: may appear normal [51]
		Advanced disease: grossly dilated and tortuous [92]

Table 4.2 (continued)

Esophageal dysmotility	Diagnostic tests	Diagnostic criteria
DES/NE	Esophageal manometry	Contractions [83]:
	Stationary/24-h ambulatory	20 to >30 % abnormal, simultaneous [61]
		Frequent, repetitive DES: ≥3 peaks; NE: >2 peaks
		Prolonged (>6 s)
		Amplitudes [95][a]:
		Primary DES: 73.4 ± 23.2 mmHg
		Primary DES: ≥180 mmHg [83]
		Primary NE: 219.8 ± 38.3 mmHg
		Pressures [81, 83]:
		UES normal
		LES normal to ↑
		May or may not have abnormal bolus transit [37]
		Abnormal reflux [81][b]:
		Reflux score: 49 ± 38
		Reference score: ≤14.7
		Chicago classification [40]:
		CFV ≥8 cm s^{-1}
	HRM	Chicago classification of NE [40]:
		CFV ≥8 cm s^{-1}
	Functional MRI	DES [41]:
		Intermittent progression of bolus
		Tertiary peristalsis
		↑ Transit time
		Corkscrew appearance
	Barium esophagogram	For DES [50]:
		Esophagus appearance:
		Puckering or beaded [61]
		Corkscrew [96] may or may not be evident [94]
		Nonperistaltic contractions [50, 94]
		For NE [50]:
		Appearances often normal
		May have tertiary contractions
NEMD	Esophageal manometry	Contractions:
	Stationary/24-h ambulatory	Amplitude of DE[c]
		<30 mmHg [50, 97]
		Nontransmitted proximal
		>30 % wet swallows [97]
		Defective LES relaxation [50, 97]
		Peristalsis [50]
		≥20 % swallows abnormal
		Normal reflux [81][b]
	Functional MRI	Not discernable [41]

(continued)

Table 4.2 (continued)

Esophageal dysmotility	Diagnostic tests	Diagnostic criteria
	Barium esophagogram	Findings nonspecific [50]
Secondary motility disorders	Barium esophagogram	Scleroderma [50]:
		↓ Or absent primary peristalsis
		Dilation of esophagus
		Patent LES
		Diabetes/alcoholism [50]:
		↓ Primary peristalsis
		↑ Tertiary contractions
		Mild dilation of esophagus [correct test?]
GERD	Esophageal manometry with impedance	*pH <4 for 15 s [33]
		Positive for DES or NE [81]
	Stationary/24-h ambulatory	Weakly acid reflux: pH falls by ≥1 unit, but remains >4 [45]
		Weakly alkaline reflux: pH increases to >7 [45]
		Acid: nadir pH to <4 [45]
		Nonacid: nadir pH to >4 [45]
	HRM with impedance	Pressures [39]:
		UES normal
		LES resting ↓
		Max. esophageal pressures:
		Normal before wet swallows [39]
		↑ Significantly after swallows [39]
		↑ During LES resting [45]
	Videofluoroscopy	
	Functional MRI	Not discernable [41]
	Barium esophagogram	Determine morphology of reflux [92, 94]:
		Esophagitis—finely nodular or granular appearance
		Ulcers—punctate or linear with halo
		Inflammation—thickened long folds
		Scarring—flattening or round, smooth stricture; "stepladder"

LES lower esophageal sphincter, *UES* upper esophageal sphincter, *EGJ* esophagogastric junction, *HRM* high-resolution manometry, *DES/NE* diffuse esophageal spasm/nutcracker esophagus, *MRI* magnetic resonance imaging, *DE* distal esophagus

[a]Values presented as mean ± SD

[b]24-h ambulatory only

[c]Values are often lower in the sitting than supine position

Esophagography is useful for evaluating the degree of gastroesophageal junction opening after endoscopic treatment of achalasia [91]. Several years following dilation or bougienage with rubber dilators, patients often require other therapies [74] for residual achalasia or persistence of clinical symptoms [82]. GERD may occur in 25–35 % of patients following dilatation [88]. Dilatation is rarely effective in adolescents and younger patients [87].

Surgical myotomy, such as laparoscopic modified Heller's transthoracic esophagomyotomy and/or partial fundoplication, is currently the definitive treatment of choice [87, 88, 93]. Heller's myotomy offers relief of symptoms in 85–100 % of patients [87]. Laparoscopic Heller's and now robotic myotomy have reduced the rate of perforations [93]. When combined with a partial fundoplication, the myotomy significantly reduces chances of resultant reflux [74, 81, 82, 87]. However, resultant scarring or incomplete initial myotomy can cause recurrent dysphagia many years later [83]. It is uncommon to treat achalasia with esophagectomy. This treatment should be reserved for advanced cases in which myotomy offers no relief [87].

Diffuse Esophageal Spasm and Esophageal Nutcracker

Etiology and Symptoms

Both diffuse esophageal spasm (DES) and nutcracker esophagus (NE) or hypertensive peristalsis [93] are rare, benign, and nonprogressive disorders with unknown etiologies (Fig. 4.4) [61]. They account for approximately 3–7 % of manometric abnormalities [98]. The disorders are classified as primary esophageal motility disorders (PEMDs) if GERD is not present [95]. However, research has shown that two out of three patients with DES or NE have GERD, even though symptoms may not correlate with reflux [95]. GERD may also play a role in triggering spasm [83, 93]. While the correlation is still unclear, treatment for

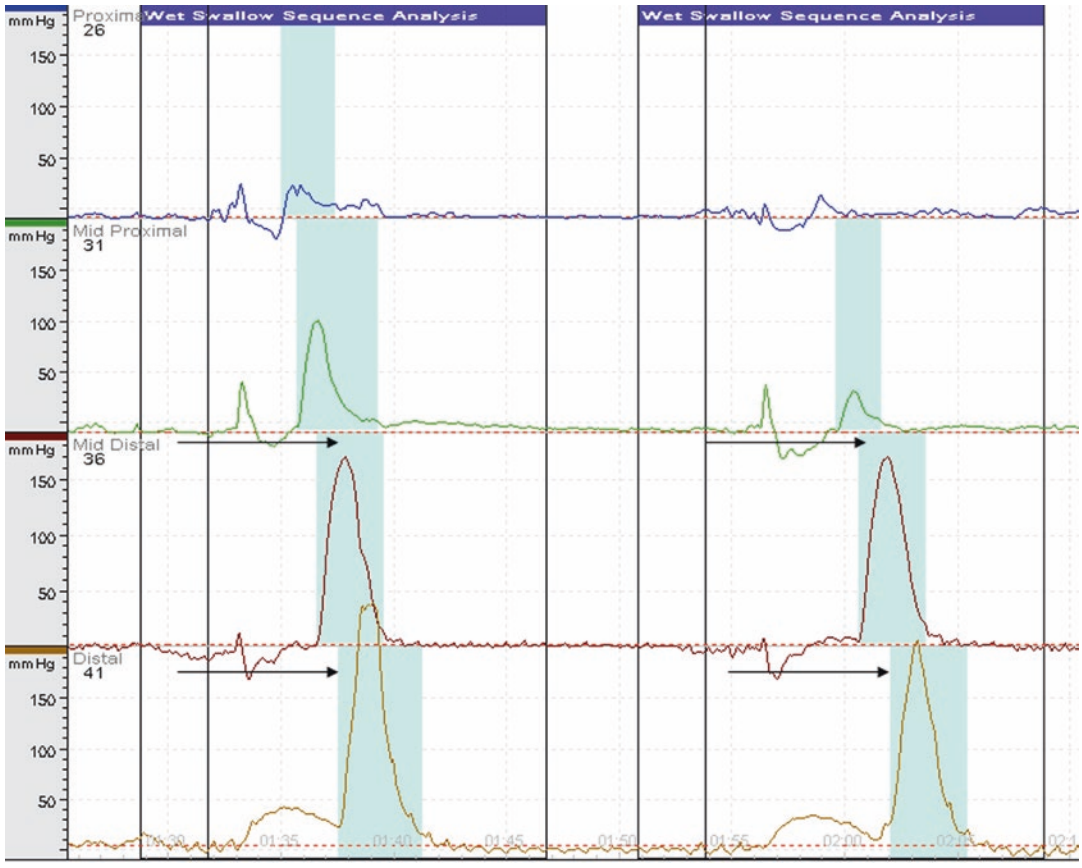

Fig. 4.4 Nutcracker esophagus. Note the mean amplitude in the distal channels (*arrows*) above 180 mmHg

reflux has reduced painful symptoms in a number of patients diagnosed with NE [83].

Manometry findings have shown that DES contractions are restricted almost exclusively to the lower third of the esophagus, which comprises smooth muscle controlled by autonomic nonadrenergic, noncholinergic neural pathways dependent on nitric oxide control. As a result, some researchers are renaming the acronym DES to distal esophageal spasm [31, 61]. Although the pathogenesis of both DES and NE is unclear, nitric oxide has been shown to be a major factor in maintaining distal esophageal peristalsis [61, 98] by mediating LES and esophageal body relaxation. This may account for the positive response in some patients to nitroglycerin and recombinant hemoglobin infusions (see "Treatment") [61]. While some researchers define DES into two types, low amplitude with less chest pain and high amplitude with more chest pain [99], others have found no distinct differences [61].

Symptoms of DES and NE are intermittent and include radiating chest pain with or without swallowing and dysphagia [50, 61, 83, 96]. Chest pain may be caused by spasms or increased contraction amplitudes during a normal bolus transit [31]. It may also be due to visceral hypersensitivity and reduce esophageal compliance [97]. Dysphagia may be due to a lower amplitude, resulting in an impaired transit [31]. Symptoms of spasm most often occur when eating or drinking, especially foods that are very hot or very cold. Pain varies in severity, ranging from mild to severe, and may last from a few seconds to several minutes [61, 83]. The intermittent, nonprogressive symptoms distinguish these disorders from achalasia and esophageal cancer [83]. NE is defined by normal peristalsis and very high intraluminal pressures [81]. Nutcracker is found more frequently in obese patients [93].

Diagnosis

Both diagnosis and treatment of DES and NE are not well defined [81], and literature recommendations vary [96]. Esophageal spasm is diagnosed using clinical symptoms and manometry, while the diagnosis of nutcracker esophagus is based only on manometry [83]. In both disorders, pH monitoring is necessary to distinguish primary motility disorder from GERD, which ensures appropriate and directed treatment [95], and an upper endoscopy will appear normal except for the presence of GERD [83]. Because healthy people often have similar symptoms and manometry readings, there is sometimes confusion regarding the diagnosis [83]. DES is marked with either high or low contraction amplitudes, while NE has high-amplitude peristaltic waves like normal peristalsis [90]. There is no presence of a corkscrew esophagus [92].

Patients with DES may have abnormal esophageal contractions in 20% [31, 95] to more than 30% [83] of wet swallows tested, although half of all patients with DES have normal bolus transit [31]. Positive manometry shows long (>6 s) frequent and repetitive esophageal contractions (≥3 peaks) [83]. Distal esophageal amplitudes can range from 73.4 ± 23.2 mmHg [95] or even exceed 180 mmHg [83]. The UES and LES usually have normal baseline pressure, although the LES pressure can be high [83], ranging from 15.7 ± 8.7 mmHg in primary DES [95]. Patients with low simultaneous and peristaltic amplitudes most likely do not have DES [99].

Patients with primary NE present with a high distal esophageal amplitude (>180 mmHg [83, 100]), even averaging up to 219.8 ± 38.3 mmHg [95]. The amplitude is slightly higher for NE in the presence of GERD (225.2 ± 52.2 mmHg) [95]. LES pressure can range from 22.7 ± 11.2 mmHg in primary NE [95].

fMRI, used in one study to diagnose DES, identified classic determinates similar to manometric and radiologic findings [41]. Other diagnostic tests, such as the barium swallow and endoscopic ultrasonography, have proven unreliable. While a barium swallow shows a "corkscrew" appearance during a contraction in patients with spasm, there is normal activity in the upper one-third of the esophagus and abnormal activity in the region of the spasm [83]. Patients with often have normal barium swallows, thereby confirming the need for manometry. Although esophageal motor disorders are associated with thickening of the esophageal muscle wall, as detected by endoscopic ultrasonography, it is unclear whether this occurs in DES [83, 96]. The thickening may

actually result from increased resistance to the bolus passage [96].

Treatment

It is not easy to treat spasm [98]. Medical and surgical approaches are palliative [82] and should be based on both bolus transit and manometric information [31]. Muscle relaxants, such as nitrates, calcium channel blockers, and Botox, have been used for esophageal spasm because they improve manometric findings and chest discomfort [74]. Calcium channel blockers, such as oral diltiazem, decrease LES pressure and inhibit peristaltic amplitude and duration [101], but pharmaceutical agents, especially nifedipine [96], may also worsen esophageal dysfunction [99] by relaxing the LES [95]. The use of these agents for DES has yet to be studied in a blinded, placebo-controlled trial [74, 98, 101].

If GERD is present, DES or NE may be considered a secondary problem, and antireflux medications are often given early in the course of treatment [83, 95]. There may be a tendency to treat symptoms with proton pump inhibitors without obtaining a pH reading. However, the result may be costly and delay appropriate treatment [95]. Anxiety and depression occur more often in patients with DES [96], and anxiolytics might be beneficial [83].

Although pneumatic dilation provides some relief, it is difficult to dilate the balloon in an effective position, rendering some dilatations ineffective. Esophageal myotomy is usually reserved for patients in whom medical therapy is ineffective because the surgery decreases the intensity but not the frequency of contractions, and it may result in dysphagia [83]. Patients who complain of dysphagia and who have a hypertensive sphincter may benefit from surgery [81]. Controlled studies on these procedures have not been done [83]. A laparoscopic Heller myotomy is the primary treatment for DES, although results of myotomy on NE are poor [81].

Nonspecific Esophageal Motility Disorders

Etiology and Symptoms

Nonspecific esophageal motility disorders (NEMDs), also known as ineffective esophageal motility (IEM) [93], are benign and nonprogressive disorders [83]. They are characterized by poor peristalsis [93] and do not appear to fit into other diagnostic categories [83, 95]. Patients may experience dysphagia and/or chest pain and have abnormal esophageal motility tracings and incomplete LES relaxation [83]. Except for abnormal contractions on manometry, patients diagnosed with NEMD often appear to have symptoms of esophageal spasm or nutcracker esophagus.

Nearly one-quarter to one-half of all patients with NEMD also have GERD, and in some studies, NEMD is a marker for GERD, especially when linked with esophagitis. This connection may be triggered by a reduced acetylcholine release from excitatory myenteric neurons to circular smooth muscle. Chronic inflammation may permanently alter neuromotor function, although acute esophagitis can be reversed [97].

The longer the segment of affected esophagus, the greater the likelihood of impaired bolus transit [97].

Diagnosis

Manometry is used to make a definitive diagnosis (Fig. 4.5) [97] and to determine the appropriate treatment for symptomatic relief [83]. In NEMDs, the bolus movement is ineffective due to low-amplitude distal esophageal contractions of <30 mmHg. The patient may also have nontransmitted proximal contractions in >30 % of wet swallows [96].

Treatment

Nonstandardized treatment is aimed at symptomatic relief, as determined by esophageal manometry [83].

Gastroesophageal Reflux Disease (GERD)

Etiology and Symptoms

GER is a very common problem in infants, although most children outgrow it by 9 months. Symptoms range from eructation to vomiting [48], and belching is common [45]. Some children have

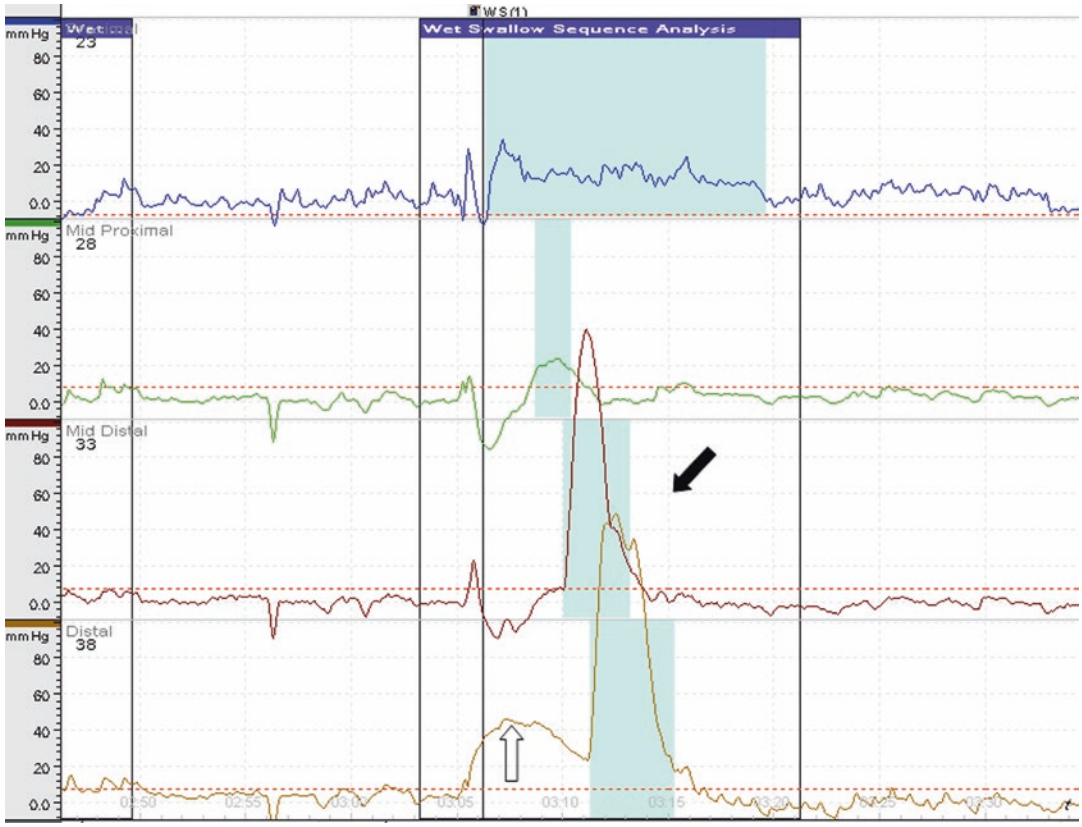

Fig. 4.5 Nonspecific abnormalities. Note the increased intrabolus pressure (*open arrow*) and the double-peaked contraction in the distal channel (*closed arrow*). *WS* wet swallow

weight loss or respiratory symptoms such as hoarseness and bronchospasm [48]. Pathologic GER is more frequently seen in children with trisomy 21, cystic fibrosis, and cerebral palsy. The majority of symptomatic reflux incidences are acidic, and 15 % are weakly acidic [45].

Diagnosis

When diagnosing GERD, it is important to coordinate reported symptoms with the analysis of reflux events. This is done by comparing the symptom index (SI) and symptom association probability (SAP) index, although controlled studies are still needed [45]. An upper GI is often done to confirm anatomic detail and exclude obstruction, such as pyloric stenosis. The upper GI also confirms a normally positioned duodenal-jejunal junction. Radionuclide studies are used to estimate reflux volume [48]. Barium esophagogram is used to determine the morphology of reflux including reflux esophagitis, peptic strictures, and carcinoma [92] (Table 4.2). Impedance-pH monitoring helps determine acid and nonacid reflux events, the extent of refluxate, and refluxate composition [45].

Fluoroscopy can be used as the only test, thereby eliminating a pH probe, if high-grade spontaneous reflux is identified [48]. The results of ultrasound correlate with pH monitoring, and the test is used to measure the length of the intra-abdominal esophagus. The shorter the esophagus, the more severe the disease [48]. During esophageal shortening, the LES is positioned above the diaphragm, thereby opposing intragastric pressure and facilitating LES opening after relaxation [45].

Patients with GERD present lower number of contractions during GER episodes, but not in the whole period [102]. HRM studies show that patients with GERD vacillate between type I

(superimposed CD and LES) and type II (CD and LES separated), with reflux usually occurring during type II [45]. However, no significant differences were found between patients with GERD and controls at stationary manometry [102].

Treatment

Initially, symptomatic GER is treated with thickened feedings. If symptoms do not improve, medications are started [48]. If symptoms persist, open or laparoscopic reflux surgery is an effective treatment [48]. The most common procedure is the laparoscopic Nissen wrap fundoplication [93], followed by the Thal and Toupet surgeries [48]. The Nissen may present complications such as a loosened wrap, which may slide down over the body of the esophagus, or a wrap that is too tight, leading to esophageal obstruction or reflux symptoms [48]. While fundoplication reduces both acid and weakly acid liquid reflux, gas reflux is reduced to a lesser extent [45].

Secondary Esophageal Motility Disorders and Others

A variety of etiologies are responsible for secondary esophageal motility disorders [49]. These include:

- Collagen vascular disease including scleroderma or systemic sclerosis
- Neuromuscular disorders
- Metabolic and endocrine disorders such as diabetes and alcoholism
- Chagas' disease, an infectious disease caused by the protozoan *Trypanosoma cruzi*

Systemic Sclerosis

Although linear scleroderma is common in children, systemic sclerosis is quite rare in this age group [103]. It is characterized by idiopathic fibrosis, which affects the esophagus in 75 % [50] to 90 % [47] of patients. Fibrosis of the smooth muscle causes atrophy in the distal two-thirds of the esophagus, resulting in esophageal dilation and an incompetent LES. Changes in the esophagus are considered a reliable indicator of disease progression [47].

The esophagus typically presents low-amplitude contraction waves and atony in the distal two-thirds [104]. Hypotonic LES is also frequent [103]. Esophageal compromise is also evident in the videofluorography, which shows the typical hypotonic esophageal dyskinesia, but also may show corkscrew esophagus, tertiary contractions, atony, dilation, and intraluminal pooling [47]. Although esophageal scintigraphy is not useful as a primary diagnostic tool, or even as a screening test, monitoring the bolus time may be useful to follow the progression of the disease [105]. The treatment of esophageal dysmotility with prokinetic agents, such as cisapride and domperidone and tegaserod, may be useful in the early stage of systemic sclerosis [106].

Progressive fibrosis of the organ may lead to shortening and, consequently, hiatal herniation. As a result, GERD is present in 90 % [47], and it may lead to reflux esophagitis, peptic strictures, Barrett esophagus, and associated esophageal adenocarcinoma [47, 50]. Dysphagia, caused by abnormal esophageal peristalsis or peptic strictures [50], chronic gastritis, and retrosternal pyrosis are common, and diagnosis may be difficult because clinical symptoms do not always coincide with the results of manometry, pH monitoring, or endoscopy [47].

Neurological and Neuromuscular Disorders

Children with cerebral palsy present decreased amplitude of peristaltic waves, lower basal pressure of LES, as well as increased frequency of simultaneous was compared to controls [107].

Patients with myotonic dystrophy may present complete contractions and normal LES relaxation, but with lower amplitude of contraction and lower UES basal tone [108]. Nonperistaltic waves after liquid swallows and simultaneous waves are common [109]. Also, the duration of the deglutitive LES relaxation is longer than in healthy subjects [110].

However, in children with progressive muscular dystrophy, UES and LES resting pressure was not different from controls, as well as contraction wave amplitude in the distal esophagus, while the lower contraction wave amplitude was found in

the proximal esophagus in children with myotonic dystrophy [111]. However, abnormalities may affect the lower esophagus, with simultaneous nonperistaltic waves [112].

Down's Syndrome

The condition is associated with disorders of the enteric nervous system, like Hirschsprung's disease and achalasia [113]. However, Down's syndrome patients also present significant more retention of radionuclide in the esophagus when compared to controls, as well as frequently abnormal manometric study, with aperistalsis, hypotonic LES, and EB dysmotility [114].

Eosinophilic Esophagitis

Dysphagia is the main symptom associated with eosinophilic esophagitis in adults and teenagers, and it may result from strictures (Schatzki's ring and stricture) and mucosal inflammation leading to mucosal thickening or dysmotility. A range of abnormalities have been reported in eosinophilic esophagitis, such as ineffective peristalsis, simultaneous high-amplitude contractions, aperistalsis, tertiary contractions, and achalasia [115]. Episodes of dysphagia are frequently associated with nonpropagated contractions and high-amplitude (>180 mmHg) contractions in children evaluated with prolonged manometry [116]. Although most pediatric patients present normal esophageal stationary manometry, abnormal stationary esophageal manometry is more frequent in patients with eosinophilic esophagitis than in patients with GERD [115, 116]. In adults, abnormalities may include all categories of manometric findings, such as aperistalsis, lower-amplitude nonpropagating contraction waves, nutcracker esophagus, and hypotensive LES [117]. Initially, the motility is normal, then hyperperistalsis develops, and it eventually evolves to low-amplitude simultaneous contractions [115].

Esophageal Injuries

After sclerotherapy for treating esophageal varices, nonpropagating contractions and simultaneous contractions can be observed in the distal third, and it may justify thoracic pain after treatment when it is not related to ulcers. LES is not affected by sclerotherapy or variceal ligation [118]. Esophageal banding ligation causes less often simultaneous contraction, while amplitude, duration, and speed of peristaltic waves are normal [118].

Caustic injuries of the esophagus may also be associated with aperistalsis and lower amplitude of contractions, but without compromising UES and LES function [119]. Abnormalities begin soon after the accident and are long lasting [120].

Congenital Disorders

Gastroschisis is associated with abnormal esophageal motility, including lower frequency of propagation of contractions, and less frequent esophageal reflexes related to infusion of bolus in the lumen. These abnormalities may play a role in the development of GERD [121].

Esophageal atresia is associated with esophageal dysmotility, although the mechanism behind is not clear. Preoperatively, normal motility has been reported, with adequate LES basal pressure, LES relaxation, and progression of contractions between proximal and distal esophagus, in spite of not being connected [122]. However, postoperatively, the anastomosis region presents no motility, while the proximal segment presents normal motility. It suggests that the coordination between the proximal and the distal esophagus is intact in not treated esophageal atresia. On the other hand, study in animal model of esophageal atresia showed that the distal atresic presents impaired smooth muscle reactivity [123]. Also, the animal model of esophageal atresia presents abnormal branching of the vagus nerve in the distal atresic segment [124]. Probably, abnormal motility in esophageal atresia results from neurological damage during surgical correction of the atresia and abnormal smooth muscle functioning. The subset of patients without vagal nerve surgical injury may present better prognosis, but further studies on motility coordination in animal model are warranted. Recently, two groups of patients have been identified: those with normal contractions in the distal part and those with aperistalsis of the distal esophagus. The last

group presents high frequency of GERD, while the first group presents better prognosis [125]. Typically, UES and LES function are normal in patients with esophageal atresia [126].

Other Diseases

Chagas' disease may be difficult to diagnose initially because manometry and radiography results mimic achalasia. *Diabetes and alcoholism*, a connective tissue disease [47], may cause decreased primary peristalsis, increased tertiary contractions, and mild esophageal dilatation [50].

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5 Vascular, Neurological and Functional Development of the Oesophagus

Udo Rolle and Alan J. Burns

The functional development of the oesophagus is closely related to the development of the oesophageal innervation and blood supply. The following chapter summarises the current knowledge in this field.

Gross Histology

The histology of the oesophageal wall shows major similarities with that of the rest of the gastrointestinal tract. There are only slight differences, i.e. only a patchy serosal layer and the lack of a mesentery. The oesophageal wall is composed of four layers: the tunica mucosa, the tunica submucosa, the tunica muscularis and the tunica adventitia.

The mucosal layer is located on the innermost side and consists of the epithelium, the lamina propria and the muscularis mucosae. The second layer is the submucosal layer, which is mainly a layer of connective tissue. This layer also contains part of the enteric nervous system (ENS), the submucosal plexus (Auerbach's plexus) as well as blood vessels. The third layer is the muscle layer, which contains the inner circular muscle and the outer longitudinal muscle. The second major component of the ENS, the myenteric plexus (Meissner's plexus), is situated between the two muscle layers. The outermost layer of the oesophagus is the adventitia, which consists of connective tissue.

Along the length of the oesophagus, there is a transition between striated muscle and smooth muscle: in the upper third of the oesophagus, the muscle is entirely striated. The second third is composed of both striated and smooth muscles, whereas in the lower third of the oesophagus, only smooth muscle is present.

Blood Supply

The blood supply of the oesophagus starts developing at the seventh week of gestation.

The arterial oesophageal blood supply can be divided into the cervical, thoracic and abdominal components [4]. These arteries are interconnected by numerous anastomoses.

The upper oesophagus (pharyngo-oesophageal transition and cervical oesophagus) is supplied by the lower thyroid artery (a branch of the thyrocervical trunk) and additional small branches of several other arteries (subclavian, common carotid, vertebral, superior thyroid, costocervical trunk).

The thoracic oesophageal blood supply is provided by branches of the aorta (paired arteries),

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the bronchial arteries and the right intercostal arteries. At the level of the tracheal bifurcation, the main blood supply comes from branches of the bronchial arteries, whereas the oesophageal branches of the aorta supply the oesophagus below the bifurcation.

The abdominal oesophagus is supplied by the oesophageal branches of the left gastric and left lower phrenic arteries. Additional blood supply may be provided by branches of the aorta, the splenic artery, the celiac trunk and the left aberrant artery [2].

The well-developed subepithelial capillary network is supplied by a distinct submucosal arterial plexus. This plexus is composed of longitudinally oriented arteries with lateral anastomosis and is formed by penetrating branches arising from a minor extrinsic plexus in the adventitia [2].

The copious blood supply and network of potentially anastomotic vessels may explain the rarity of oesophageal infarction.

The dense submucosal venous plexus of the upper oesophagus drains into the superior vena cava. The veins of the proximal and distal oesophagus drain into the azygos system. Collaterals of the left gastric vein, a branch of the portal vein, receive venous drainage from the mid-oesophagus. The submucosal connections between the portal and systemic venous systems in the distal oesophagus form oesophageal varices in cases of portal hypertension.

Lymphatic Drainage

Most of the lymphatic fluid of the oesophagus drains directly to the juxta-oesophageal lymph nodes. Additional lymphatic drainage is provided by the lung lymph nodes and the diaphragmatic lymph nodes.

Innervation

The oesophagus is dually innervated; that is, it is innervated by both intrinsic and extrinsic nerves. This specific innervation pattern is responsible for the oesophageal peristalsis.

Like other parts of the gastrointestinal system, the oesophagus is governed by the autonomic nervous system (enteric nervous system, ENS). In addition to this intrinsic nervous system, an additional extrinsic nervous system is present. Both systems are relevant for swallowing and oesophageal peristalsis.

The Oesophageal ENS

The enteric nervous system (ENS) starts from the most oral part of the oesophagus and extends along its complete length down to the stomach. There are notable differences between the oesophageal ENS and the ENS of the remaining gastrointestinal system (GI).

In general, the oesophageal ENS, particularly the submucosal plexus, seems less developed than the ENS in the rest of the gastrointestinal tract [13].

The proportion of nitrergic myenteric neurons seems to be much higher within the oesophageal ENS. Nitrergic myenteric neurons comprise up to 55 % of all myenteric oesophageal neurons in humans [10], with the greatest number of these neurons within the abdominal segment of the oesophagus. Another specific finding is the remarkable coexistence of nNOS with other neuropeptides (vasoactive intestinal peptide, galanin and neuropeptide Y) in the human oesophagus [10].

Previous investigations have clearly demonstrated region-dependent overall neuronal loss of 22–62 % in the human oesophagus during ageing [8]. This neuronal loss is more pronounced in the upper oesophagus.

Development of the Oesophageal ENS in Humans [3, 12]

Vagal (hindbrain) neural crest cells migrate into the oesophagus at gestational week 4. These cells migrate in an oral-to-anal direction, reaching the distal stomach at week 5 and colonising the entire length of the GI tract by week 7.

Neural and glial differentiation can be detected at week 7 within the foregut using PGP9.5 and

S-100 staining, respectively. These neurons and glial cells are present in the presumptive myenteric plexus close to the serosal layer. The first neuronal and glial cells are found within the submucosal layer at week 9. From weeks 9 to 12, the submucosal plexus of the foregut increases in size.

At week 7, the myenteric plexus consists of a few closely packed neurons and glia. The myenteric plexus increases in size, and the respective neurons and glial cells become less packed from week 12 to 20.

Development of the Foregut ENS [12]

Week 4	Neural crest cells (NCCs) scattered within the dorsal foregut mesenchyme
Week 5	NCCs within the dorsal foregut start to coalesce and form chains
Week 6	Numerous NCCs within the stomach
Week 7	Numerous NCCs external to the oesophageal circular muscle organised into distinct ganglia (Fig. 5.1)
Week 8	Ganglia present external to the oesophageal circular muscle
Week 8	NCCs at the internal aspect of the oesophageal circular muscle

The activity of the oesophageal ENS is modified by sympathetic and parasympathetic innervation.

Sympathetic Innervation

Preganglionic sympathetic nerves arise from the anterior mediolateral cell columns of the T1 to T10 spinal cord segments. Sympathetic innervation of the oesophagus is provided by postganglionic fibres, which are sympathetic nerve fibres originating from the cervico-thoracic ganglion (ganglion stellatum) of the thoracic celiac and the cranial thoracic ganglia (ganglia thoracica II–V). These postganglionic fibres reach the oesophageal wall and synapse with submucosal and myenteric neurons of the ENS.

Activation of sympathetic innervation leads to inhibition of oesophageal peristalsis and inhibition of the secretory activity of oesophageal glands.

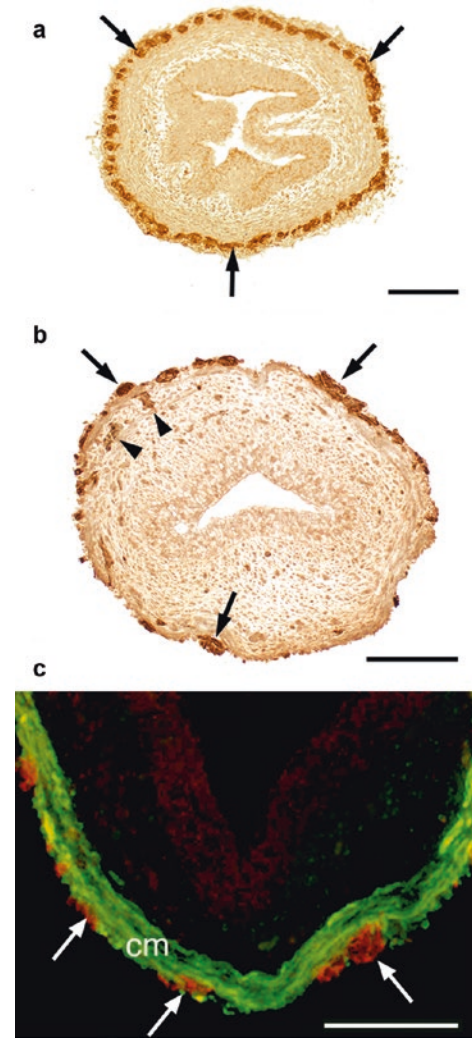

Fig. 5.1 Development of neural crest-derived enteric nervous system (ENS) and smooth muscle in the human oesophagus. (**a**) At week 7 of development, neural crest cells, as shown by p75NTR-immunostaining (*brown*), were present external to the circular muscle layer (*arrows*) in the region corresponding to the presumptive myenteric plexus. (**b**) At week 8, neural crest cells were distributed around the periphery of the gut wall (*arrows*), external to the circular muscle layers. Occasional immunopositive cells were also present internal to the circular muscle (*arrowheads*) in the region corresponding to the presumptive submucosal plexus. (**c**) At week 8, the circular muscle layer (*cm*) was well developed, and a dense band of cells was strongly immunopositive for alpha smooth muscle actin (*green*). p75NTR-positive neural crest cells (*red*) were grouped into presumptive ganglia (*arrows*), external to the circular muscle. Scale bar = 100 um (**a**, **b**) and 50 um (**c**) (Reproduced with kind permission from Springer Science+Business Media B.V. from original article by Wallace and Burns [12] (Modified from Figs. 3, 4, and 6))

Parasympathetic Innervation

Preganglionic parasympathetic neurons originate from the dorsal vagal complex located in the dorsomedial hindbrain medulla. The dorsal vagal complex consists of two nuclei, the nucleus tractus solitarius and the dorsal motor nucleus of the vagus.

The parasympathetic innervation of the upper oesophagus is from the recurrent laryngeal nerve, while in the lower oesophagus parasympathetic innervation is from the vagus nerve. Below the tracheal bifurcation, the trunks of the left and right vagal nerves form the oesophageal plexus within the adventitial layer.

The axons of the preganglionic parasympathetic neurons are carried via the vagus nerve and synapse on postganglionic neurons within the enteric nervous plexus.

Functional Considerations/ Oesophageal Peristalsis [9]

Peristalsis within the skeletal muscle of the oesophagus results from sequential activation of the neurons by the vagal centres (nucleus ambiguous), whereas peristalsis of the smooth muscle part of the oesophagus is mediated by the vagal dorsomotor nucleus and the intrinsic myenteric plexus [5]. The phasic smooth muscle of the oesophagus receives intramural inhibitory innervation (i.e. by nitric oxide) and excitatory innervation (mediated by acetylcholine). The mechanism of peristalsis within the oesophagus appears to be complicated and is not completely understood. It has been shown that the oesophagus, in contrast to the remaining intestine, is able to generate a primary peristalsis. Generally, one assumes that peristalsis within the striated and smooth muscle parts of the oesophagus is due to sequential activation of cholinergic excitatory nerves. Furthermore, it has been shown that a gradient of the contraction wave exists due to the latency of the contraction along the oesophagus. This latency gradient might be related to nitric oxide-mediated inhibitory innervation [1]. It has been demonstrated that inhibitory innervation seems to be denser within the lower oesophagus than in the upper oesophagus.

Furthermore, it has been shown that an increase in cholinergic stimulation delays the latency of contraction in the proximal oesophagus, which is under greater cholinergic control than the distal oesophagus. This phenomenon results in a loss of peristalsis [6]. Peristalsis in the longitudinal muscle layers seems to be mediated at the level of the dorsomotor nucleus of the vagus nerve [7, 11].

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Part III

Esophageal Atresia Spectrum

The Spectrum of Esophageal Atresia

6

John E. Foker

The spectrum of esophageal atresia (EA) is commonly portrayed as comprising four basic types [1] (Fig. 6.1). This general classification satisfactorily illustrates the main configurations of EA lesions that may be encountered in affected babies. It does not convey, however, the many variations that may occur within the types nor the treatment complexities that may arise from them.

Defects Found in the EA Spectrum

The Primary Defect

An atresia of part of the esophagus is, of course, the primary and necessary defect in the EA spectrum. The site of the atresia predictably occurs at the level of the lower trachea, although there is considerable variation in how much esophagus is missing. The absent portion of esophagus creates upper and lower esophageal segments separated by a variable gap. The gap may range from negligible when the upper and lower segments are fused, to very long when the lower segment is only a primordial nubbin on the wall of the stomach at the site where the esophagus originates.

Gap length is the most important practical consequence of EA. The ease of achieving a successful primary esophageal anastomosis and, in turn, a good long-term outcome is primarily determined by the relative gap length [3, 4]. The significance of the gap length will be in the eye of the beholder; nevertheless, as it increases from 2 to 3 cm and beyond, an initial primary anastomosis will be increasingly difficult. From the literature, a 3 cm gap is generally considered long, and a primary anastomosis will have a greater likelihood of complications including leaks and later strictures [3–5]. Certainly, gap length guidelines are only relative, and a 3 cm gap in a 3-year-old does not have the same significance as one in a small newborn. The use of esophageal growth induction, moreover, has provided great flexibility and allowed this length and even longer gaps to be reliably repaired [6]. A reliable repair, nevertheless, always requires careful construction of the anastomosis to ensure a good result [7].

When EA is the only significant lesion and there is no associated tracheoesophageal fistula (TEF), it leaves blind upper and lower esophageal pouches, and this configuration, type A, begins the classification (Fig. 6.1).

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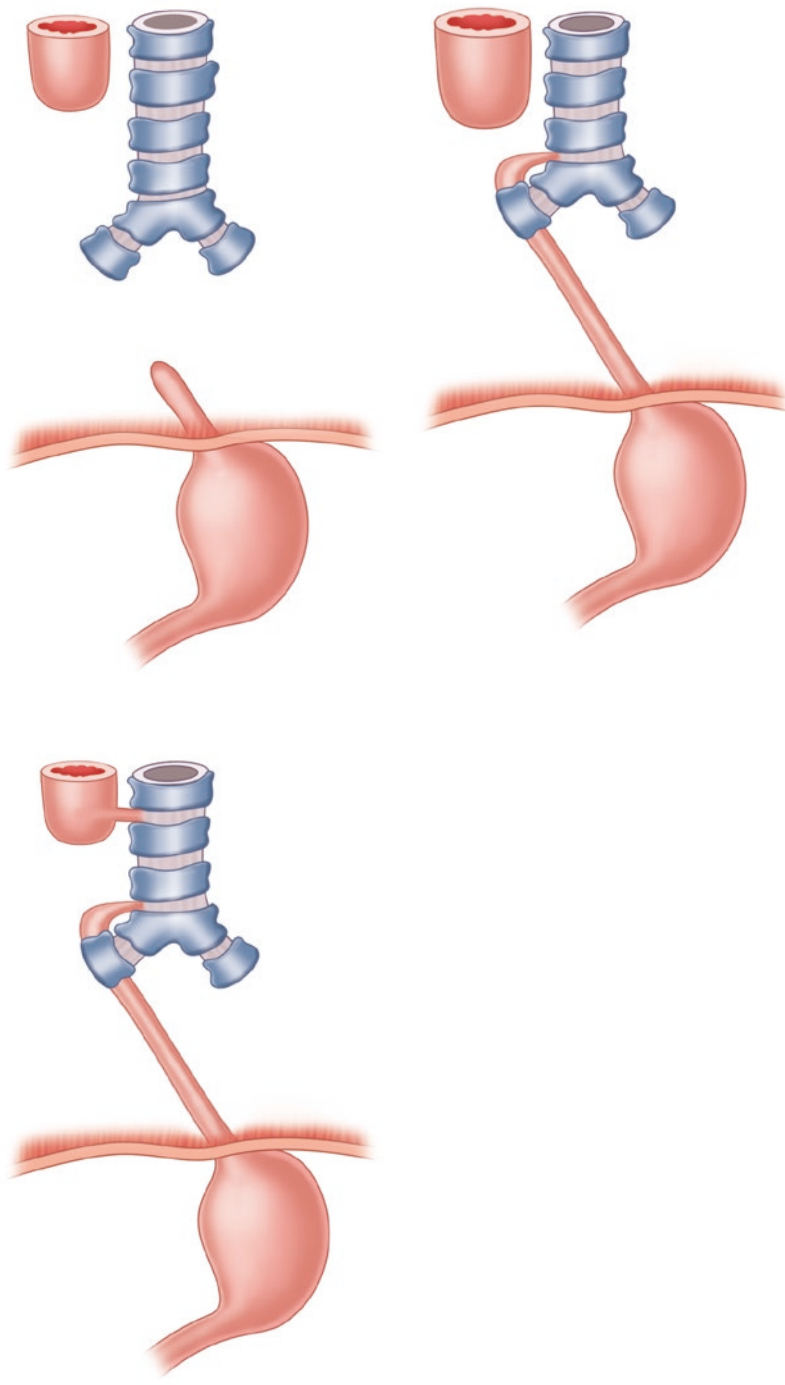

Fig. 6.1 This classification of EA is commonly, but not universally, used. Gross [1] proposed this grouping based on the earlier work of Vogt [2] and others. The necessary defect is atresia of the esophagus and with this alone is type A EA. In the next three types, the occurrence of a tracheoesophageal fistula (TEF) into the upper, lower, or both esophageal segments completes the groupings

The Major Secondary Defect

A tracheoesophageal fistula (TEF) is the next most important defect, and this occurs in most cases of EA. When present, its location broadens and fills out the spectrum, also often adding complexity for surgeons and interventionists. A TEF may be into the upper, lower, or both esophageal

segments and creates the other major types (B, C, and D), respectively, within the EA spectrum [1].

An upper pouch TEF produces type B EA, and it is usually located relatively high into the upper thoracic trachea, while the lower segment is unattached as in type A. This, in turn, means the unattached lower esophagus may vary greatly in length with an inversely resulting gap length.

The most common EA lesion by far, however, has a lower segment which ends as a fistula into the trachea and together with a blind upper pouch is the configuration of type C EA. A fistula into both the upper and the lower segments rounds out the general classification with the rare configuration (type D) (Fig. 6.1).

Tertiary Defects

The major groups are not uniform, however, and a variety of other less important lesions add to the considerable variety and complexity found in the EA spectrum. Some of these additional lesions may make a primary repair more difficult, while others may make it easier.

The additional lesions include double atresias; multiple TEFs; cords between the lower segment and the upper segment, the airway, or the mediastinum; and other rare variations [8]. In general, tertiary lesions which increase the effective gap length will make an anastomosis more difficult, while those that shorten it will make a primary repair easier. Often they may not affect gap length as in a double TEF and require only a slightly more involved repair. A missed TEF, however, may produce significant continuing symptoms and subsequently may be difficult to diagnosis and repair.

The goal of this chapter will be to describe the EA spectrum in more detail and include the implications for the ease of accomplishing a primary anastomosis.

Previous Recognition of the EA Spectrum

Our understanding of the EA spectrum has been shaped by a long antecedent history. A description of the EA malformation appeared at least as early as 1670 with the report by William Durston of a blind upper pouch in a baby that succumbed shortly after birth [9]. In 1697, Gibson described the common form of EA (type C) in greater detail and later published the case [10]. Unfortunately, these lesions could not be successfully repaired for almost another three centuries.

The first collection of EA cases published in 1905 by Kreuter began to indicate the breadth of the EA spectrum [11]. The more systematic description by Vogt in 1929 was helpful to Gross in constructing the classification described that is still commonly used today (Fig. 6.1) [1, 2].

More variations continued to be reported in case reports and small series, and in 1976 they were compiled into an Atlas of Esophageal Atresia by Kluth [8]. The atlas diagrammatically illustrated the 54 variations that had appeared in the literature and put them into categories which provided an increased understanding of the breadth of the EA spectrum. The categories in the Atlas, although logical, do not correspond to the current classification; for example, both type I and type II would now be considered type A. The atlas, nevertheless, is very interesting and useful for the clear diagrams of the many unusual lesions that had been found and described by that time.

The classification proposed by Gross [1] also included two additional groups that were without EA: one for an isolated tracheoesophageal fistula (TEF) and another for esophageal stenosis [1]. The TEF in the former group is typically located relatively high near the junction of the cervical and thoracic trachea and considered an H- or N-type TEF.

The isolated stenosis is usually found at about the junction of the middle and lower thirds of the esophagus and may be produced by one of several mechanisms: a simple web, aberrant rests of bronchial or pancreatic tissue or from an isolated, thick knot of dysplastic, fibromuscular tissue.

The lesions of these two additional, and seemingly unrelated, groups have a fairly predictable location which suggests they may also result

from a relatively constant developmental error or, much less likely, because of a secondary genetic influence. Atresia is not part of these otherwise very different groups, and they will not be included in this discussion of the EA spectrum.

Variation Within the Main Types of the EA Spectrum

For all infants with EA, the reparative goal is to establish continuity with the stomach. Continuity can be accomplished in one of several ways; however, the emphasis at the University of Minnesota has been on a true primary esophageal repair. We have defined a true primary repair as an esophageal anastomosis leaving the gastroesophageal (GE) junction below the diaphragm, where it belongs, and without doing esophageal myotomies to increase length bur which disrupt the integrity of the esophageal wall and may lead to a diverticulum [6].

An initial true primary repair may be difficult in some cases; however, the ability to induce esophageal growth makes an anastomosis eventually possible in virtually all patients. Rather than using the fallback approach of a replacement or interposition graft, the small, blind segments of esophagus can be reliably grown and a true primary repair carried out. Before or, at least, during the initial operation, the recognition of the anatomic details of an unusual and difficult EA defect will increase the likelihood of developing a successful surgical plan. A true primary repair should always be the goal, how it is accomplished, of course, will be influenced by the EA variations encountered.

This chapter, therefore, will present the EA spectrum in greater detail beginning with the classification proposed by Gross [1] and identify the characteristics which may affect the ability to accomplish a primary repair (Fig. 6.1). This information should make the difficult case more understandable and less daunting, which will increase the likelihood of achieving a good and durable outcome.

Type A EA (Fig. 6.2)

EA with a blind upper and lower esophageal pouch (type A) is conceptually the most straightforward and begins the classification. The atretic site typically occurs in the mid-esophagus; however, when the patient is born, the upper and lower segments may be of substantially different sizes. A blind upper pouch tends to be enlarged by the attempts at swallowing saliva in utero, while the size of lower esophagus may be quite variable and will mainly determine the gap length. The repair, therefore, may differ substantially in ease of accomplishment. These lesions

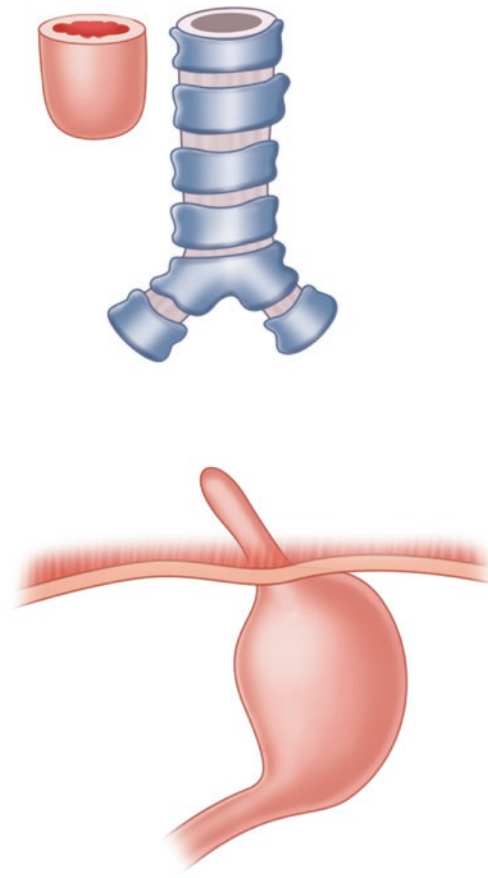

Fig. 6.2 Type A is the first group and consists of EA without other significant lesions. As will be discussed, the lower segments vary greatly in size and make this outwardly simple group quite variable in configuration and clinical difficulties

vary from the easiest to the most difficult defects in which to accomplish a primary esophageal anastomosis while maintaining the GE junction below the diaphragm.

Variations Which Increase Gap Length in Type A EA

Small Lower Segments

Lower segment size is the most important determinant of gap length. Growth usually lags when the lower segment is not attached in some way, even with a cord, to either the upper esophagus or the airway. If the lower segment is unattached, the axial tension provided by the growing spinal column (which provides the biomechanical growth signal) will not be effectively transmitted, and the distal esophagus may remain small. Although it is often unclear what constitutes effective attachment, the wide variation found in lower segment size is illustrated by expanding the type A defects pictured within the classification. The subtypes A_1, A_2, and A_3 attempt to convey the range in size and morphology of the lower esophageal segments in these defects (Fig. 6.3). This variation, in turn, will determine the difficulty in accomplishing an esophageal anastomosis.

The lower segment size range, however, is even greater than shown. The smallest will be a primordium barely discernible on the northwest quadrant of the surface of the stomach, while the largest lower segment will abut the upper pouch. Between these extremes will be a continuum of sizes and difficulties in repair. For examples of the spectrum and the corresponding methods of repair.

Second Atresias

A second atresia in either the upper or lower pouch effectively lengthens the gap because the true lumen stops well short of the apparent end of the segment. An unrecognized second atresia was present in one case in the Minnesota experience in which the upper pouch was put on axial tension (traction) in the usual fashion to induce growth. Unfortunately, more growth occurred in the distal portion of the upper pouch which did not have a satisfactory lumen. When this was discovered, the distal portion was trimmed away, and the shorter true upper segment was put on traction. After sufficient upper pouch growth occurred, a successful true primary repair was carried out.

Variations Which Decrease Gap Length

An Atretic Cord

The lower segment may have an atretic cord arising from the end and reaching higher in the posterior mediastinum or even to the airway or upper pouch [8]. As the spinal column lengthens, the cord may transmit tension to the lower segment in utero enhancing its growth. An atretic cord can be helpful during the initial thoracotomy when it is found in the posterior mediastinum, deep to the vagus nerve. The cord should be grasped and divided, and by pulling up the inferior end, the lower esophageal segment can be delivered upward and dissected free down to the esophageal hiatus. When a cord is present, the lower segment will typically be at least 2–3 cm in length and not a tiny primordium. Granted, a 2–3 cm long lower segment would be very unsuitable for an initial true primary repair; however, it will be quite satisfactory for placement of traction sutures.

Fusion of the Esophageal Segments

Occasionally the upper and lower esophageal segments are fused to some degree, although there is no luminal continuity. This configuration eliminates concerns about the gap and makes a primary repair much easier.

Type B EA

Type B EA has a TEF from the upper pouch into the high thoracic trachea and a blind lower segment (Fig. 6.4). Very rarely, there may be two upper pouch fistulas [8]. The upper pouch fistula, in turn, tends to drain the saliva and reduces the tendency for a large upper segment. The fistulas are relatively

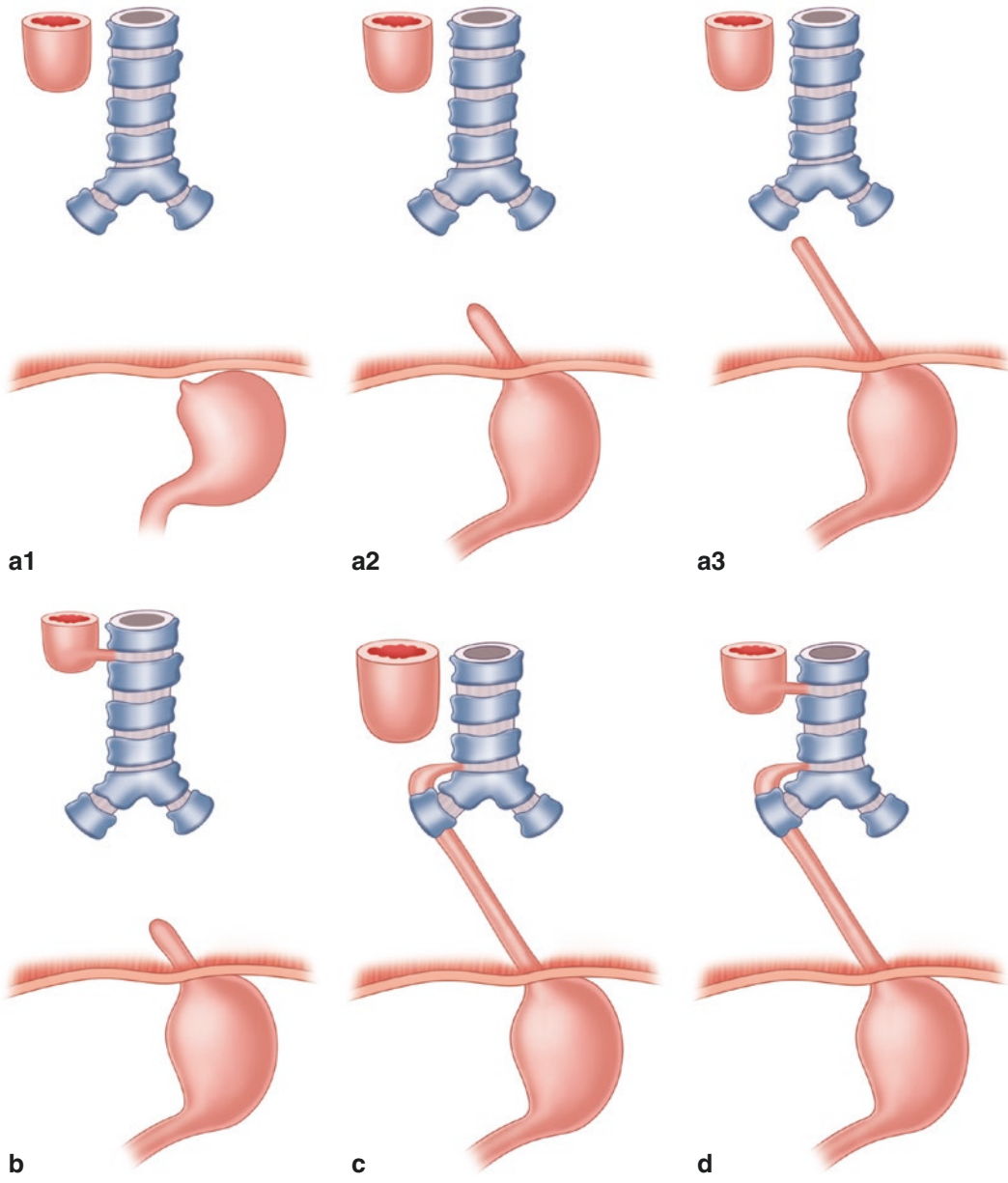

Fig. 6.3 This expanded classification portrays a range of lower segment size in type A EA. The segments pictured range from an esophageal primordium ($\mathbf{A_1}$) to a relatively long lower esophagus ($\mathbf{A_3}$). In reality, however, the range is even wider with a lower segment not discernible on preoperative studies or one abutting the upper esophageal pouch

small; nevertheless, the upper pouches are usually smaller than expected.

Of importance, the lower segment size should be highly variable and resemble the type A lesions. Although only a few examples have been described in any detail, lower segment size will be a consequence of effective attachment to spinal column growth; therefore, their length should vary consid-

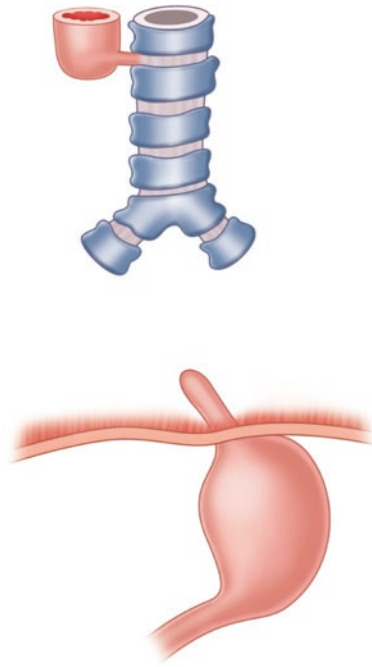

Fig. 6.4 Type B EA. The upper pouch has a TEF and may be relatively small. The lower segment is unattached and therefore should vary widely in size

erably. A portrayal of lower segment size that resembles the type A EA lesions has been created (Fig. 6.5).

Variations Which Increase Gap Length

Upper Pouch TEF

The upper fistula drains saliva into the trachea, and the pouch tends to be smaller than in the type A and type C lesions. A smaller upper pouch will increase the gap length.

More than one upper pouch TEF could increase drainage and further hinder upper pouch growth. Although small series of this unusual lesion have been reported, the upper pouch size was not given [9, 10].

Unattached Lower Segment

When the lower pouch is not attached to either the airway or the upper esophageal segment, it is not reliably subjected to the axial tension supplied by spinal column growth. If the investing fibers around the lower segment are relatively loose and do not effectively transmit the axial tension to the lower segment, it will remain small and the gap will be long.

Variations Which Decrease Gap Length

Larger Upper Pouch

The upper pouch TEF may be very small, however, and therefore saliva swallowed in utero may effectively enlarge the upper pouch and make it as large as in type C EA [9, 10].

Attachments to Lower Segment

Attachments (e.g., a cord) to the upper esophagus or trachea from the lower segment would provide tension as the spinal column lengthens and stimulate pouch growth and reduce gap length. The few reports of type B EA, however, have not described this variation nor the anastomotic consequences.

Type C EA (Fig. 6.6)

Type C EA with a blind upper pouch and a TEF from the lower segment to the trachea is by far the most common form encountered and makes up 70–85 % of the EA cases in most series.

For pediatric surgeons, this is a favorite congenital defect to repair. Because the lower segment usually reaches the lower trachea, most type C defects are initially primarily repairable; nevertheless, keeping the GE junction below the diaphragm may occasionally pose difficulties.

Variations Which Increase Gap Length

Lower Insertion of TEF

The principal variation which increases gap length is a low insertion of the distal esophageal segment into the airway. Usually, the TEF inserts directly into the lower thoracic trachea and provides adequate length for an initial true primary repair. If the insertion is into the undersurface of the carina or into the right or even left main stem bronchus,

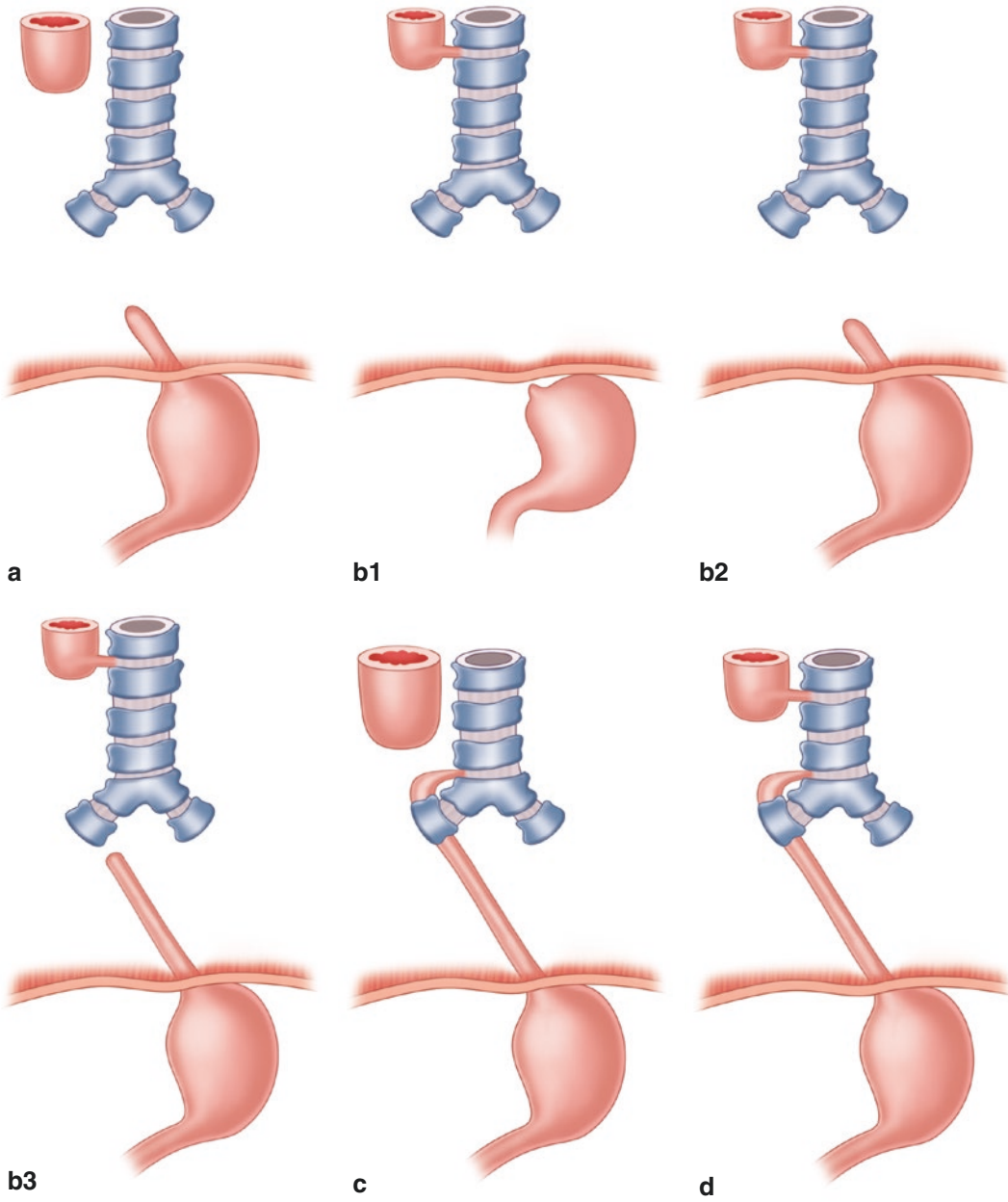

Fig. 6.5 The usually unattached lower segment in type B EA leads to a variety of possible sizes as shown by the B_1, B_2, and B_3 configurations

however, the gap between the divided TEF and the upper pouch will be increased. Even though the upper pouch is undrained by a TEF and is typically large in type C lesions, a low insertion of the TEF may provide difficulties for a primary repair.

If the gap length raises uncertainties for the surgeon, the lower segment fistula should be divided, closed, and placed, along with the upper pouch, on a period of internal traction to stimulate growth. Each end should be anchored into

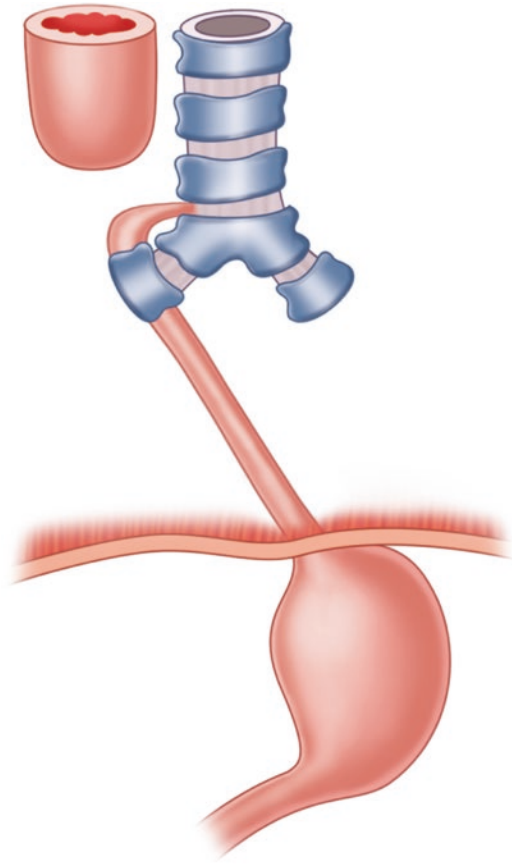

Fig. 6.6 Type C EA. Type C EA is, by far, the most common configuration. The upper pouch is relatively large, and the lower segment usually enters the trachea making a configuration usually suitable to an initial true primary repair

the prevertebral fascia under tension which will provide the biomechanical signal. A period of growth will allow a better anastomosis to be created without resorting to myotomies or a partial gastric pull up.

Aortic Arch Anomalies (Aberrant Subclavian Artery, Vascular Ring, and Right Aortic Arch)

Anomalies of the aortic arch will often be associated with increased gap length and could occur with any of the EA types. The reports, however, are predictably with the much more common type C EA lesions. An aberrant right subclavian artery from a left aortic arch will lie between the upper and lower segments and may be associated with a longer gap. One series reported several cases and this anatomy made the repair more difficult but still possible. Although the aberrant vessel may appear to be influencing the gap, it is unlikely to be directly increasing gap length because this vascular anomaly occurs more commonly with an intact normal esophagus. A similar, albeit more unusual, circumstance could exist in the presence of a right aortic arch, an aberrant left subclavian artery and EA.

Complete vascular rings are the most difficult form of these arterial anomalies to treat. The aortic ring may be completely produced by the double aorta or one composed of the ascending aorta, a retroesophageal transverse arch, and a left descending aorta in which the ring is completed by the ductus arteriosus. The ring must be divided, and, whatever its configuration, the anterior component must be moved forward to relieve tracheal compression. After the mobilization is completed, the esophageal ends are either placed on traction or an esophageal the anastomosis carried out.

A right aortic arch will make the esophageal repair more difficult through a right thoracotomy incision. The difficulty in repair comes more from the presence of the descending aorta in front of the anastomotic site rather than an increased gap length, although this can also occur. Surgeons vary as what approach they would use. The author would choose a left thoracotomy in order to make the very important esophageal anastomosis as straightforward as possible.

Variations Which Decrease Gap Length

High Insertion of a Large TEF

If the lower segment remains large virtually up to the trachea and inserts higher than usual, the conditions will be more favorable for a primary repair. These variations are not discussed in reports, however, and are only accepted with gratitude.

Fusion Between Upper and Lower Pouches

Occasionally, the upper and the lower pouches are touching or even fused. Gap length would not be a problem; however, the openings should be generous to reduce the likelihood of a later stricture.

Type D Esophageal Atresia (Fig. 6.7)

The rare type D lesions have two TEFs, one from the upper pouch into the posterior aspect of the trachea and one from the lower esophageal segment lower into the airway. This is a rare lesion, infrequently reported and probably comprising only 1 % of the EA spectrum.

The factors which increase or decrease the gap length will resemble those for the upper pouch in type B lesions and for the lower segment in type C EA. For the potential effects on the gap lengths, see also the discussions of the type B and C EA lesions. The actual occurrence and consequences of anatomic variations which will affect gap length, however, have not been reported but can be predicted.

Variations Which Increase Gap Length

A large TEF will more effectively decompress the upper pouch, and it will remain smaller and higher, increasing the gap.

If the lower fistula inserts into the underside of carina or a mainstem bronchus as opposed to the trachea as commonly occurs in type C lesions, the gap would be increased.

Variations Which Decrease Gap Length

A small upper segment fistula will impede drainage, leading to a larger pouch. Similarly, a lower TEF which is larger and inserted higher will improve the configuration for a primary anastomosis.

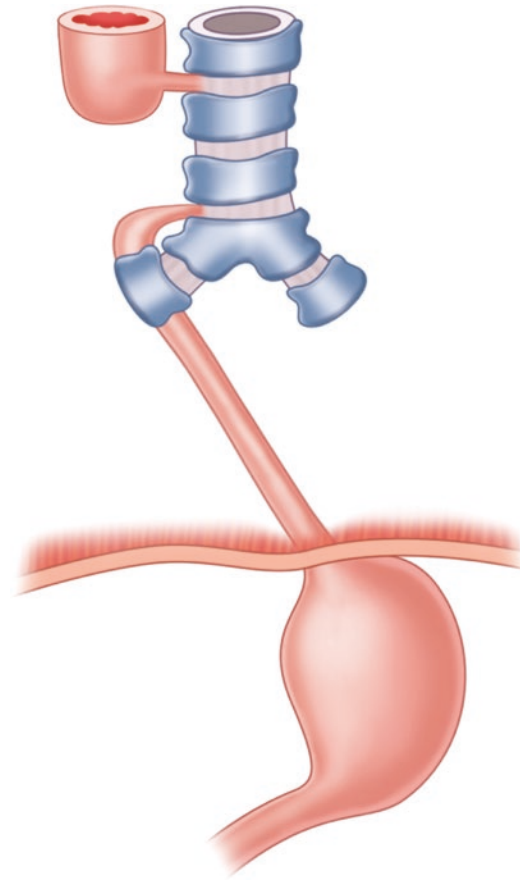

Fig. 6.7 Type D EA. A very rare lesion in which both the upper and lower esophageal segments are connected to the air way, usually the trachea as shown, but the proximal portion of a mainstem bronchus may be the terminus for the lower esophagus

Summary

As experienced pediatric surgeons know, the variety in EA will be even greater than illustrated in this chapter. Within the EA groups will be a continuum of lesions that range from more easily repairable to those defects that are essentially impossible to initially repair primarily. The success of an EA repair will largely be determined by the length of the gap between the upper and lower segments; however, other variations in the anatomy of the EA defect may also influence the outcome.

The recognition of the favorable or unfavorable characteristics of these defects should aid an understanding of the implications for repair. EA repair is certainly not in its final form now, and this chapter should stimulate further thinking about EA and lead to improved outcomes. Finally, consideration of the EA spectrum reveals the developmental

variety produced by Nature, which enriches the surgeon and those who care for these infants.

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7 Esophageal Atresia and Tracheoesophageal Fistula: The Clinical Spectrum, Diagnosis, and Evaluation

Justin D. Klein and Russell W. Jennings

Introduction

The embryologic formation of the esophagus is complete following recanalization around the tenth week of fetal life. Any irregularity in the developmental process may result in a variety of malformations, including but not limited to esophageal atresia with or without a tracheoesophageal fistula. Knowledge of the anatomic and clinical spectrum of esophageal malformations, as well as the relationship with other organ systems, is essential for the surgeon to assess and diagnose these lesions. This chapter reviews the spectrum of disease, associated anomalies, and diagnostic evaluation which begins with prenatal evaluation.

Anatomic Spectrum

Interruption in the normal development of the esophagus and trachea may result in a wide variety of esophageal malformations. These congenital anomalies range from pure esophageal atresia, to esophageal atresia with tracheoesophageal fistula (either proximal or distal), to an isolated tracheoesophageal fistula. Before the development of successful surgical repair of esophageal atresia and tracheoesophageal fistula, affected infants died from bronchopneumonia and dehydration within the first weeks of life [1]. Improvement in surgical skills and knowledge, the advent and availability of antibiotics, and superior intensive care skills have led to greater success taking care of the neonate. Today, virtually all infants with esophageal atresia without severe associated anomalies survive infancy.

Accounts of esophageal atresia date back to 1670 with William Durston's report "A Narrative of a Monstrous Birth in Plymouth" in which a blind-ending upper esophageal pouch was described in the right-sided infant of female thoracopagus conjoined twins [2]. The next report of an infant with esophageal atresia and tracheoesophageal fistula can be found in the 6th edition of *The Anatomy of Human Bodies Epitomized*. Thomas Gibson described both the clinical and anatomic features of the most common type of esophageal atresia in 1697 where he explained the infant's attempts at feeding resulted in convulsive choking [3]. Confirmatory postmortem findings included a blind upper pouch with a distal tracheoesophageal fistula. After this time, numerous references appeared in the literature, but there were no reported survivors for the next 250 years.

Throughout the 1800s case reports of esophageal atresia and tracheoesophageal fistula emerged,

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including one with an infant afflicted with esophageal atresia, tracheoesophageal fistula, and associated rectal agenesis with rectourinary fistula [4]. Harald Hirschsprung published four cases of his own in Copenhagen and collected ten cases of esophageal atresia and distal tracheoesophageal fistula from the literature in 1861 [5]. Years later Morell McKenzie reported 57 cases of congenital esophageal malformations with 37 examples of tracheal or bronchial esophageal fistula in 1880 and suspected these lesions were not extremely rare. He also discussed at length the embryology, pathology, and clinical diagnosis of these anomalies, including a description of associated anomalies such as spina bifida, horseshoe kidney, and imperforate anus [6]. Reports in the literature up to 1919 accounted for 136 verifiable cases of esophageal atresia, 92 of which had associated tracheoesophageal fistula [7].

The history of the approach to classification of esophageal atresia reflects differences in the terminology but not in the types of anomalies encountered. The first proposal to gain acceptance was that of Vogt in 1929 that recognized four main categories [8]. Type 1 was total agenesis of the esophagus, admittedly rare. The second referred to esophageal atresia without accompanying tracheoesophageal fistula. Type 3 described esophageal atresia accompanied by tracheoesophageal fistula and was further subdivided to describe the location of the fistula. Type 3a referred to esophageal atresia with a proximal tracheoesophageal fistula, type 3b was used to describe esophageal atresia with a distal tracheoesophageal fistula, and type 3c was esophageal atresia with tracheoesophageal fistula between both esophageal segments and the trachea. The last, type 4 described a tracheoesophageal fistula with an intact esophagus.

With the accumulation of operative experience, many other anatomic classifications of esophageal atresia were proposed. In 1944 Ladd emphasized that atresia of the esophagus occurs more frequently than previously considered, and he introduced a numeric form of classification that consisted of five types of esophageal atresia denoted by Roman numerals [9]. Gross subsequently changed the numeric system in 1953 to an alphabetical one that is still widely used [10] (Fig. 7.1). Type A refers to esophageal atresia alone and accounts for 7.8 % of anomalies. Type B occurs in 0.8 % of patients and includes esophageal atresia with an upper pouch fistula. Esophageal atresia with lower pouch fistula is denoted by the letter C and is the most common with 85.8 % of cases. Type D is the least common at 1.4 % and is esophageal atresia with both upper and lower fistulas. A tracheoesophageal fistula without atresia accounts for 4.2 % of anomalies and is denoted by type E. The last, type F, is not commonly grouped with atresias and describes esophageal stenosis [11]. Subsequent classification schemes based on prevalence did not gain widespread acceptance, and neither did Swenson's proposal to return to a numeric classification using Arabic numerals instead of Roman numerals [12, 13].

Using a large number of case descriptions from 1673 to 1973, in 1976 Kluth classified tracheoesophageal defects into 10 types and 88 subtypes [14]. Kluth's classification suggests that any imaginable configuration of esophageal atresia and tracheoesophageal fistula has happened or may happen. Kluth's findings may be summarized as follows: among lesions of the middle esophagus, atresia is more common than stenosis; tracheal fistula accompanies most atresias; and the fistula is usually from the lower esophageal segment in the presence of an atresia, but from the cervical esophagus when no atresia is present.

More recently, classification schemes have faded with the recognition that the critical surgical features are omitted from most of them. One of the most important pieces of information for the surgeon is the length of the gap between segments. The common form of blind upper pouch and lower fistula may be technically difficult to put together when the ends are far apart, or very straightforward when close together. The distance between esophageal segments can range from negligible, as is the case when the segments are separated by only a membrane, to ultra-long gap, where a distance of 3 cm or more is found [15–18]. One should also be suspicious of the possibility of an additional upper fistula no matter the initial classification. A full description of the important anatomic details of the malformation is more desirable than fitting it into a classification scheme. Classification attempts are also

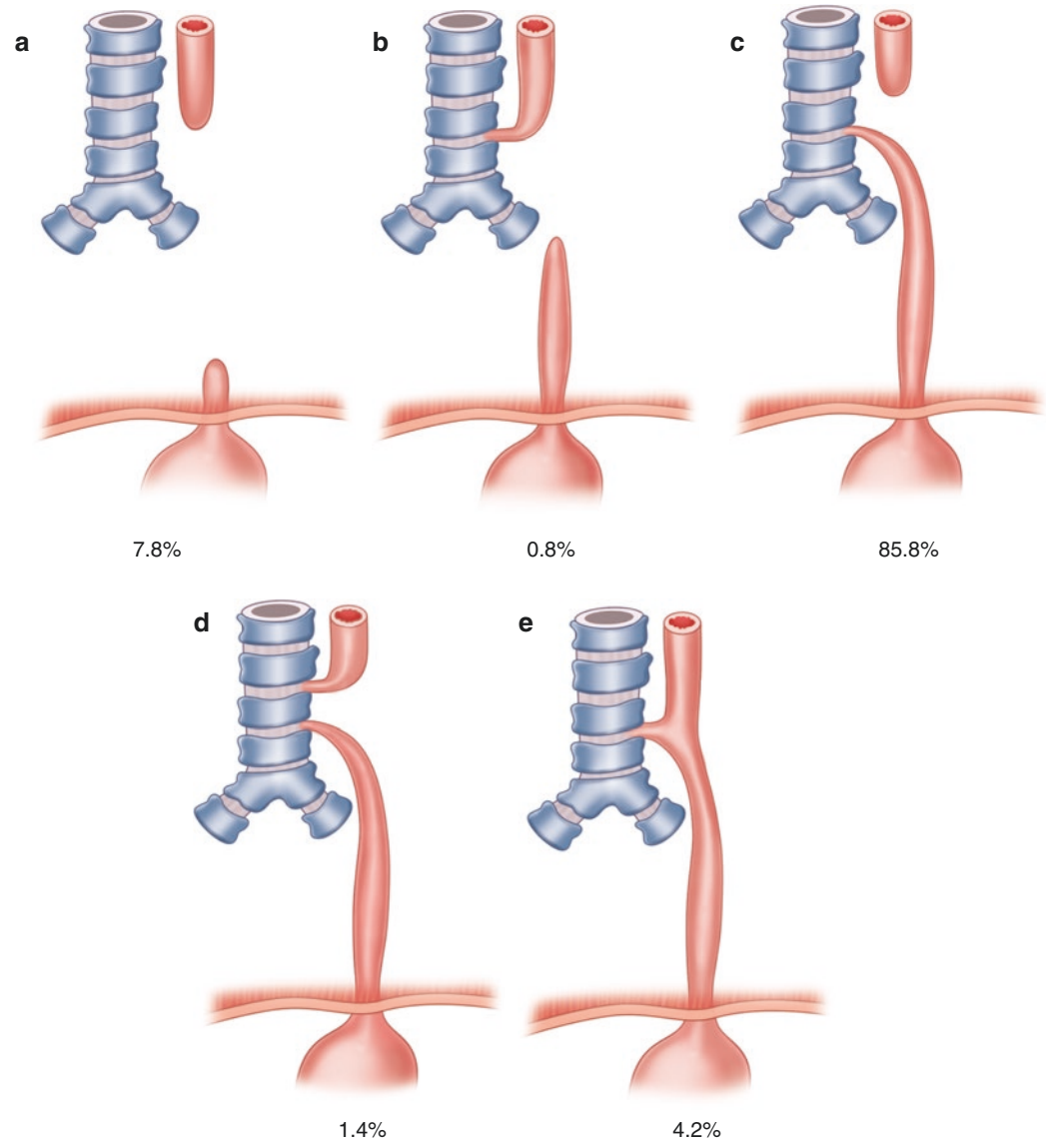

Fig. 7.1 Gross classification of anatomic patterns of esophageal atresia. (**a**) Esophageal atresia without a tracheoesophageal fistula. (**b**) Atresia with a proximal tracheoesophageal fistula. (**c**) Esophageal atresia with a distal tracheoesophageal fistula. (**d**) Esophageal atresia with both a proximal and distal fistula. (**e**) Tracheoesophageal fistula without atresia (From Gross [10])

incomplete because of the numerous anatomic variations of esophageal atresia. Although some types could be grouped together and a few were esophageal duplications rather than atresias, it is apparent that the esophageal atresia spectrum is wide ranging. In spite of the above statements, the surgeon must keep in mind that variations, even among the most common type, may require that changes in procedure be adopted for each particular patient.

Clinical Spectrum

In contrast to anatomic classifications, a classification scheme based on the infant's clinical condition was proposed by Waterston in 1962 (Table 7.1). It has proven useful to predict survival among infants with EA. This risk stratification allowed comparison of case outcomes over time and between hospitals [19]. Infants were grouped by birth weight, severity of pneumonias

Table 7.1 Waterston risk groups

Group	Survival (%)	Waterston classification
A	100	Birth weight >2,500 g and otherwise healthy
B	85	Birth weight 2,000–2,500 g and well or higher weight with moderated associated anomalies (noncardiac anomalies plus patent ductus arteriosus, ventricular septal defect, and atrial septal defect)
C	65	Birth weight <2,000 g or higher with severe associated cardiac anomalies

Table 7.2 Spitz classification

Group	Survival (%)
I. Birth weight >1,500 g without major congenital heart disease	97
II. Birth weight <1,500 g or major congenital heart disease	59
III. Birth weight <1,500 g and major congenital heart disease	22

if present, and associated congenital anomalies. Not surprisingly, survival was found to be very good for large (>2,500 g), healthy babies (group A), but remained poor for premature infants weighing less than 1,800 g (group C). Classification into the intermediate group was based on either an intermediate weight of 1,800–2,500 g, moderately severe pneumonia, or a significant anomaly that meant a larger baby would be at greater risk. Significant birth defects or severe pneumonia would also move a larger baby into group C. Today, severe associated cardiac anomalies and preoperative ventilator dependence, rather than pneumonia, are the major preoperative determinants of mortality and may well define a more current group C [20, 21].

Attempts to improve survival in Waterston group C infants have to some extent mirrored the surgical techniques of the pre-survival era. Division of the stomach was proposed for some group C infants when thoracotomy was considered too risky. This approach allows control of the tracheoesophageal fistula and provided a gastrostomy without producing reflux and without incurring the risks of a thoracotomy [22, 23]. Perhaps a better solution is the simpler and more effective technique of transthoracic fistula ligation, which has been successfully used on many occasions in low-birth-weight, critically ill infants [24, 25]. Currently, infants at high risk are nourished by hyperalimentation and decompressed by gastrostomy. If ventilation is compromised or alimental nutrition is desired, the fistula is ligated so the infants can be maintained until they are in suitable condition for repair of the esophageal atresia.

The Waterston classification is routinely used to compare results between centers caring for affected infants; however, many investigators have questioned its current validity [20, 26, 27]. Increased numbers of low-birth-weight infants are surviving, neonatal critical care continues to improve, and more treatment options are available for infants with multiple congenital anomalies. Because of these advances, several new classification systems have been proposed. One of the first was suggested around the fiftieth anniversary of the first successful primary anastomosis for esophageal atresia with tracheoesophageal fistula. It suggested refining Waterston's classification based on the overall physiologic status of the infant with esophageal atresia without regard to weight, gestation, or pulmonary condition. More frequent and earlier primary repairs were performed while maintaining excellent survival rates compared with infants previously managed using Waterston's criteria [26].

One of the most commonly used systems resulted from a review of 357 cases of esophageal atresia over 12 years. Spitz discovered that birth weight and major cardiac disease are the most important predictors of survival [28] (Table 7.2). Other prognostic classifications have been proposed, including one suggesting only severe pulmonary dysfunction with preoperative mechanical ventilation requirement, and severe associated anomalies were independent predictors of survival. It also reflected the more favorable outcome of low-birth-weight neonates [20]. The measured length of the esophageal gap also provides a method of classification to predict morbidity, long-term outcome, and costs associated with esophageal atresia and tracheoesophageal fistula surgery [29].

Despite the advances in surgical technique and repair of esophageal atresia with or without tracheoesophageal fistula, survival of the infant depends more on improved methods of caring for neonates in the intensive care unit. Survival of the infant depends on efficiently minimizing airway contamination by oral and gastric secretions and facilitating enteral nutrition. This is evidenced by the newer prognostic classifications proposed, reviewing variables that are independent predictors of survival. Effective repair continues to aim to control the upper pouch and eliminate any fistula present to prevent aspiration while the stomach is accessed for ongoing enteral nutrition.

Incidence

There is sizable variation in the frequency at which esophageal atresia and tracheoesophageal fistula have been reported over the years. Combined, these anomalies occur at an incidence of approximately 1 in 3,000 to 1 in 4,500 births [30–34]. Over the years, studies have documented a slight male predominance for esophageal atresia. This has been statistically quantified with a male-to-female ratio of 1.26, whereas the normal population sex ratio is 1.06 [35]. There is also an increased risk for esophageal atresia with a first pregnancy and there is a slight increasing trend in the rate of esophageal atresia with advanced maternal age [34, 35]. There has been no evidence for a difference in the incidence of esophageal atresia with pregnancies induced by in vitro fertilization [36].

Multiple reports of affected siblings in the same family, as well as one of a father having two children affected by esophageal atresia by different wives, have been published [6, 37–39]. Esophageal atresia with tracheoesophageal fistula has also been noted in a parent and child, as well as cases spread over multiple generations [40–42]. Children with successful repair of these defects have now reached reproductive age and will be interesting to observe their effect on population studies. Twinning among infants with esophageal atresia has been frequently reported and rates are higher, ranging from 6 to 9 % of cases compared with 1 % of twinning in the general population [35, 38, 39, 43, 44].

Early observations regarding familial esophageal atresia and tracheoesophageal fistula were presented with the belief of a developmental rather than genetic origin [30]. However, chromosomal anomalies are also relatively frequent, occurring in 6.6 % of infants with esophageal atresia. Anomalies include trisomy 13, trisomy 18, the VACTERL association, Pierre Robin sequence, Holt-Oram syndrome, and DiGeorge syndrome [35, 45]. Multiple studies have also described transverse and vertical familial cases of each variety of esophageal atresia [40, 45–48].

It has been postulated that the development of esophageal atresia is not a genetic phenomenon, but a developmental environmental incident because identical twins originate within 2 weeks of fertilization, and the trachea and esophagus develop 2 weeks later [49]. Various environmental agents have been implicated as teratogens in the pathogenesis of esophageal atresia. Esophageal atresia has occurred in children born to mothers with prolonged exposure to estrogen and progesterone during pregnancy as well as prolonged exposure to contraceptive pills [50, 51]. Additionally, esophageal atresia has been reported in some infants of diabetic mothers, after intrauterine exposure to thalidomide, and in the setting of infectious hepatitis [49, 52].

All things considered, esophageal atresia is usually sporadic and appears to have multiple heterogeneous and complex causes. Evaluation of the risk statistics reported in the literature to date suggests a 0.5–2 % recurrent risk among parents of one affected child. This number increases to 20 % if more than one sibling is affected. The empiric risk of an affected child born to an affected parent is 3–4 % [45]. Evidence to date suggests both developmental environmental and genetic causation. Sporadically, a fistula without esophageal atresia escapes detection in the neonatal period. Several such cases have been reported in children and even more remarkable are those which remain undiscovered until adulthood [53–55].

Table 7.3 Incidence of associated anomalies

Anomaly	Incidence (%)
Cardiovascular	~35
Genitourinary	~24
Gastrointestinal	~24
Neurologic	~12
Musculoskeletal	~20
VACTERL association	~20
Overall incidence	50–70

Associated Anomalies

The clustering of anomalies in esophageal atresia infants has long been recognized (Table 7.3). The associated anomaly often alters treatment and affects survival – especially cardiovascular anomalies and when multiple anomalies are present and frequently the infant weighs less than 2 kg [56, 57]. The widely used VATER association acronym was created to incorporate vertebral defects, anorectal malformations, tracheoesophageal lesions, and renal or radial anomalies that tend to occur together [58–60]. The most common of all associated defects are hemivertebrae, which along with the less frequent rib and sternal anomalies are associated with longer esophageal gaps [61]. The term association was introduced to include a nonrandom occurrence of a number of malformations, suggesting that several organ systems are similarly susceptible to a disruption of normal mesodermal induction and development [58].

Cardiovascular complications are commonly present in infants with associated anomalies and also the principal cause of death in the majority of these children [57]. To include this important group of lesions, the mnemonic has been altered to the VACTERL association by the addition of cardiac and limb defects [62–64]. A proposed reorganization to ARTICLE (anal, renal, tracheoesophageal, intestinal, cardiac, limb, etc.) had been suggested as an easier acronym to remember, but has not been generally accepted [65]. The appearance of any of the characteristic VACTERL defects should stimulate a search for other such defects. Esophageal atresia is also often found in conjunction with the CHARGE association (coloboma, heart defects, atresia choanae, developmental retardation, genital hypoplasia, and ear abnormalities) [66, 67].

Other less well-described and infrequent conditions connected with esophageal atresia include the Schisis association (omphalocele, neural tube defects, cleft lip and palate, and genital hypoplasia), unilateral pulmonary agenesis, cleft lip and palate, deafness, microcephaly, omphalocele, and multiple other syndromes [45, 64, 68–74]. Online Mendelian Inheritance in Man lists 23 entries involving esophageal atresia.

Prenatal Diagnosis

Prenatal diagnosis of structural congenital anomalies permits prompt neonatal management and may avoid potential hazards associated with diagnostic delays. It also prepares parents for the birth and intensive postnatal management of their baby [75, 76]. The first sign of esophageal atresia in the fetus may be polyhydramnios, which occurs with approximately 33 % of mothers with fetuses with esophageal atresia and distal tracheoesophageal fistula and with virtually 100 % of mothers with fetuses with esophageal atresia without fistula. Polyhydramnios can result from the inability of the fetus to swallow and thus absorb amniotic fluid. This mechanism has been demonstrated in fetuses with esophageal atresia by injecting saccharine into the amniotic sac and failing to recover it in the maternal urine [77].

Obstetrical ultrasound findings of a subjectively small or absent stomach bubble with polyhydramnios are suggestive of esophageal atresia and tracheoesophageal fistula [78–80].

The finding of only a small or absent stomach bubble is known to have a high false-positive rate [80, 81]. Healthcare providers should be alerted by this finding to search further for other ultrasound features of anomalies associated with esophageal atresia and tracheoesophageal fistula such as those of the VACTERL association and CHARGE syndrome discussed earlier [82–84]. Prenatal detection rates on ultrasound are around 45 % when esophageal atresia is an isolated anomaly.

However, interpretation of findings suspicious of esophageal atresia and tracheoesophageal fistula must be done cautiously, especially when other anomalies are noted at the same time [85].

An "upper pouch sign" was first visualized by ultrasonography and reported in two cases with polyhydramnios and absence of the stomach bubble in 1983 [86]. Subsequently, several investigators have used ultrasound to visualize the blind-ending upper esophageal segment in the neck and mediastinum during fetal swallowing [79, 84, 87–91]. The ultrasonographic finding of an anechoic area in the middle of the fetal neck in association with polyhydramnios and a small stomach may increase the accuracy of prenatal diagnosis of esophageal atresia, but is an inconsistent finding.

Magnetic resonance imaging (MRI) has been used to confirm prenatal ultrasound findings and assist in the identification of fetal thoracic lesions [92, 93]. Reports have varying results based on the MRI criterion for diagnosis of esophageal atresia and tracheoesophageal fistula. If non-visualization of the esophagus alone was used as criterion, there would be an unusually high proportion of false-positive results [94]. Others require the distinction of an absent stomach bubble, but employ the MRI scan as a complement to the sonographic evaluation [93–95].

Postnatal Diagnosis

Postnatal suspicion of esophageal atresia and tracheoesophageal fistula is frequently prompted by the observation of excessive salivation in the first few hours of life. The addition of coughing, choking, and/or cyanotic spells when the first feedings are initiated and inability to pass a tube through the mouth or nose into the stomach should also raise suspicion and prompt further evaluation. Clinically, infants with tracheoesophageal defects present with well-differentiated symptoms depending on the type of defect encountered.

In the case of esophageal atresia without tracheoesophageal fistula, the diagnosis of esophageal atresia should be suspected when unswallowed saliva is noted in the infant's mouth and nostrils at birth. If enteral feeds are attempted, the milk will be regurgitated and not coagulated, having never reached the stomach. Coughing and choking are usually less consistent than when a proximal fistula is present and cyanosis is less severe. Failure to pass a suction catheter through each nostril or mouth into the stomach almost confirms the diagnosis and should be documented with a chest radiograph. There will be no gas visualized in the bowel with pure esophageal atresia (Fig. 7.2). Aspiration of saliva and feeds will result in pneumonitis, and there will be no lanugo (swallowed hair and skin cells) in the meconium.

The presence of a proximal fistula to esophageal atresia alters the presentation to include more severe choking and coughing spells, as saliva and any feedings given have direct access to the tracheobronchial tree. The infant may have periods of cyanosis resulting from intermittent laryngeal

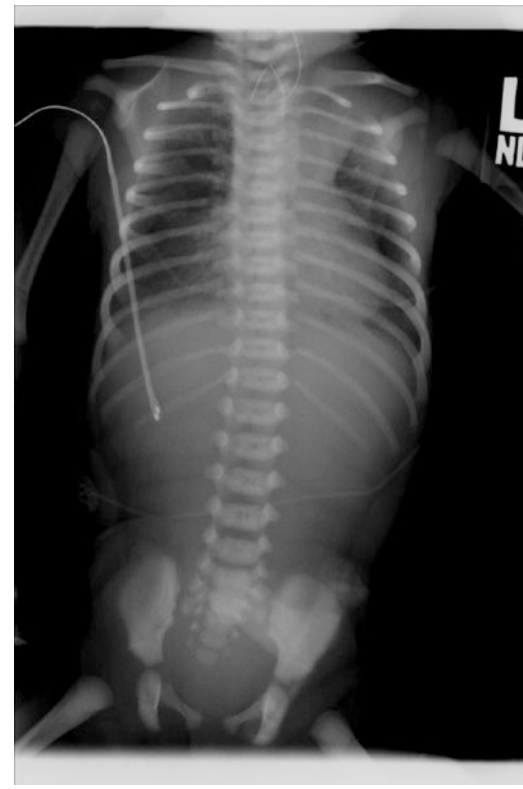

Fig. 7.2 Coiled nasogastric tube in the proximal esophagus with absence of intestinal air suggests isolated esophageal atresia without a tracheoesophageal fistula

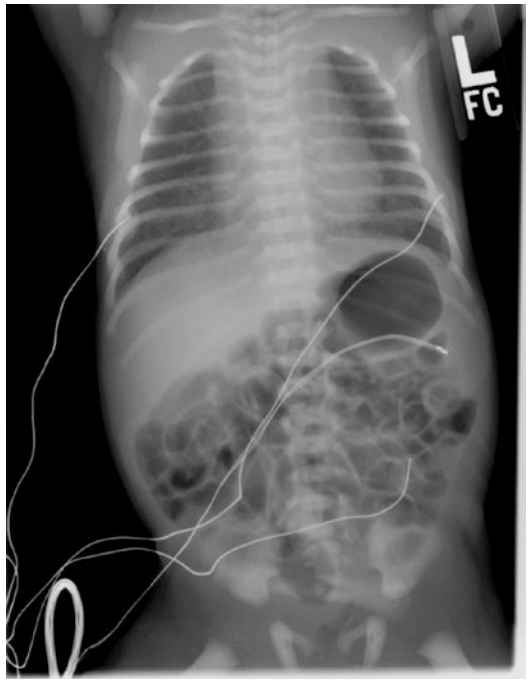

Fig. 7.3 Coiled nasogastric tube in the proximal esophagus with the presence of intestinal air suggests esophageal atresia with a tracheoesophageal fistula

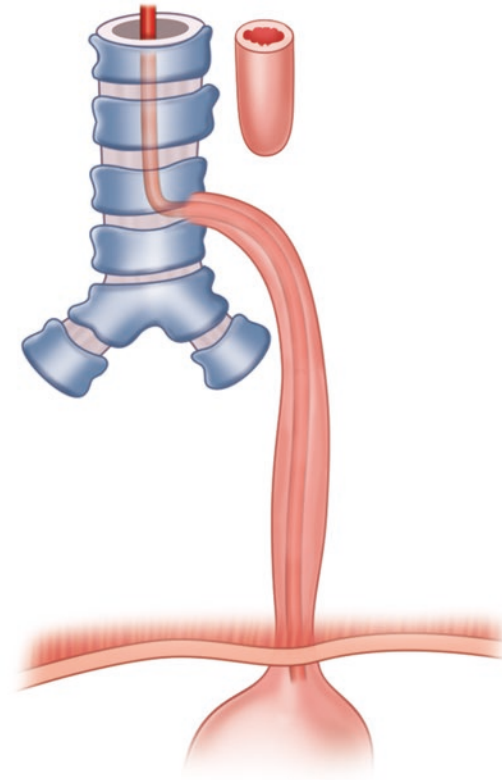

Fig. 7.4 Catheter passing through the tracheobronchial tree and entering the distal tracheoesophageal fistula

spasm. A nasal catheter may be passed via the fistula into the airways, but radiographically will be confirmed to not be below the diaphragm. There will similarly be no air noted in the gastrointestinal tract. Severe pulmonary compromise may ensue if this type is not recognized quickly.

Esophageal atresia with isolated distal tracheoesophageal fistula may present similarly to the infant discussed above with esophageal atresia without tracheoesophageal fistula. However, radiographs will demonstrate air within the gastrointestinal tract (Fig. 7.3). Another consideration will be GER through the distal esophageal fistula into the airways and gastric distension resulting in inability to ventilate. Additional considerations in the immediate neonatal period result from abdominal distention as the latter will be accentuated if bagging the infant at the time of birth is necessary. Pulmonary compromise can be significant as gastric fluid passes retrograde through the distal fistula and enters into the trachea and lungs, producing a chemical pneumonitis. A distended abdomen also elevates the diaphragm, placing pressure on the lungs, reducing compliance, and worsening pulmonary function. The aforementioned aspiration of saliva from the upper pouch into the trachea further exacerbates pulmonary compromise.

Infants with esophageal atresia and both proximal and distal fistulas present similarly to those with only a proximal fistula, resulting in respiratory distress and symptoms primarily from the fistula of the upper segment. Additionally, the distal segment can lead to more severe pneumonitis as the gastric contents have access to the trachea from retrograde flow as previously discussed. A nasal catheter may end up in the tracheobronchial tree and radiographs will demonstrate air in the bowel as well with this type of fistula [96] (Fig. 7.4). In theory, the catheter may also pass directly from the proximal fistula into the distal fistula and end up in the stomach providing a false sense of security or suggesting the presence of an H-type fistula (Fig. 7.5).

The presence of symptoms and their severity among the H-type fistula are governed by the size of the fistula. Widely patent fistulas may allow

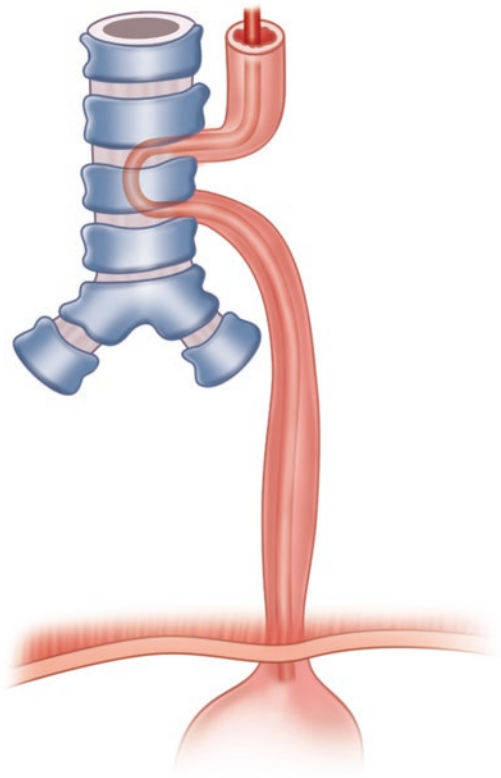

Fig. 7.5 Catheter passing through both the proximal and distal fistulas

enough esophageal contents to enter the trachea and these infants will present similarly to those with esophageal atresia and a proximal fistula. Smaller communications may result in repeated bouts of pneumonitis and/or pneumonia as well as a persistent cough. This type of fistula must be kept in mind when assessing older children and adults with chronic respiratory complaints, especially bronchiectasis of unknown etiology [97]. When evaluating a neonate for recurrent pneumonia, the differential diagnosis should include diseases like agammaglobulinemia, cystic fibrosis, and neurogenic dysfunction of the esophagus. Additionally, mechanical complications related to esophageal stenosis, congenital hiatal hernia, or tracheal compression by vascular rings must be ruled out.

Finally, isolated esophageal stenosis without tracheoesophageal fistula is often clinically insignificant. Symptoms depend on the diameter of the stenotic segment. Regurgitation of feeds and failure to thrive are the most common presenting symptoms and may be exacerbated by the introduction of solid food. As undiagnosed children become older, dysphagia becomes the primary presenting complaint. If the stenotic segment produces significant proximal dilation, tracheal compression may occur. Although pulmonary symptoms are uncommon, aspiration pneumonitis is always a danger if frequent vomiting develops. It has been suggested that an etiologic factor of esophageal stenosis is failure of epithelialization, based on the denuded mucosal linings of stenotic segments [98]. However, embryologically the earliest manifestation of the esophagus is an epithelial tube, and the absence of epithelialization must have only been acquired secondarily [99].

Diagnosis and Evaluation of the Esophagus in Infants

A clinical diagnosis may be confirmed by esophageal catheterization, x-ray examination with or without contrast media, and esophagoscopy or bronchoscopy. Esophageal catheterization is easily accomplished with a soft #10 French catheter. Failure to pass the catheter beyond 12 cm or having the catheter return out the nose or mouth suggests a proximal atresia. A chest x-ray at this time will support the diagnosis by demonstrating the radiopaque tube curled in the proximal segment or the tip of the catheter resting in the superior thorax (Figs. 7.2 and 7.3). Chest radiographs may confirm the presence of pneumonitis and suggest the length of the upper pouch by the location of the curled catheter tip. In rare circumstances with a double fistula, the catheter may pass down the trachea into the distal fistula ending up in the stomach. This situation may lead to a delay in diagnosis and be dangerously misleading.

Esophageal perforation after a traumatic intubation may mimic esophageal atresia [100–103]. Attempts to pass a catheter into the stomach fail due to an extra esophageal pouch or because swelling has closed off the esophagus. Esophageal injury may mimic esophageal atresia on esophagogram either as a pseudodiverticulum secondary to a contained cervical perforation or as esophageal

obstruction from compression of the lumen by the mass effect created by a false passage [104, 105].

Radiographs of infants with the existence of a distal fistula usually reveal a distended, air-filled stomach and intestines. Typically the location of the fistula will be just above the carina but may enter either of the mainstem bronchi, thus lengthening the gap. Often, there is associated atelectasis from upward pressure on the diaphragm. The absence of gastrointestinal gas suggests a pure atresia or an atresia with an associated proximal fistula. There is also at least one case report of a gasless abdomen resulting from an obstructed distal tracheoesophageal fistula [106]. Other information gleaned from evaluating chest and abdominal radiographs includes heart size, pulmonary vascularity, abdominal gas patterns, the presence of pneumonia, and evidence of vertebral and rib anomalies. Rarely necessary, computed tomography (CT) and magnetic resonance imaging (MRI) have been used if the esophageal segments could not otherwise be identified.

Contrast medium may be added to better assess the length of the upper pouch and determine if an upper fistula is also present. Even with a seemingly normal esophagus, the presence of a small fistula, particularly an H type, cannot be ruled out. Upper fistula findings are often subtle, and in one series the diagnosis was made with equal frequency before, during, and after repair of the esophageal atresia [107].

Air contrast will assist in visualizing the anatomy and contrast agents will also help distinguish between a stenotic segment and achalasia with cardiac stricture as the cause of the regurgitation. While the use of contrast agents should be generally avoided, when needed, a small amount of dilute barium, 1–2 cc, administered under fluoroscopy is usually adequate for diagnostic purposes, and the contrast should be aspirated from the existing catheter at the completion of the study (Fig. 7.6). Barium is well tolerated in the airway, while water-soluble agents with an osmolality greater than 240 are contraindicated due to the high osmotic load which causes severe pneumonitis if it enters the tracheobronchial tree.

Radiographs and contrast studies may suggest the diagnosis of esophageal atresia with tracheoesophageal fistula, but bronchoscopy and/or esophagoscopy is often required to confirm the diagnosis. Bronchoscopy has been helpful in demonstrating proximal tracheoesophageal fistulas, as well as discovering the presence of unusual lesions or determining tracheobronchitis and tracheomalacia [108] (Fig. 7.7). Esophagoscopy and bronchoscopy may add to the amount of preoperative information and provide the simplest method of excluding the presence of a proximal fistula, if adequate skill levels are present in the anesthesia and surgical teams.

In the diagnostic evaluation for esophageal atresia, associated recognizable defects must be excluded which could influence the choice and timing of operative repair. The diagnosis of ano-

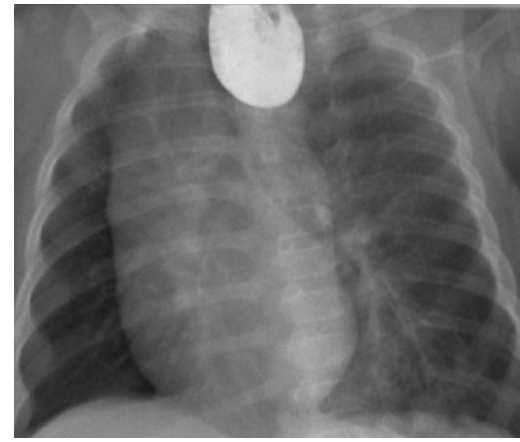

Fig. 7.6 Barium fluoroscopy

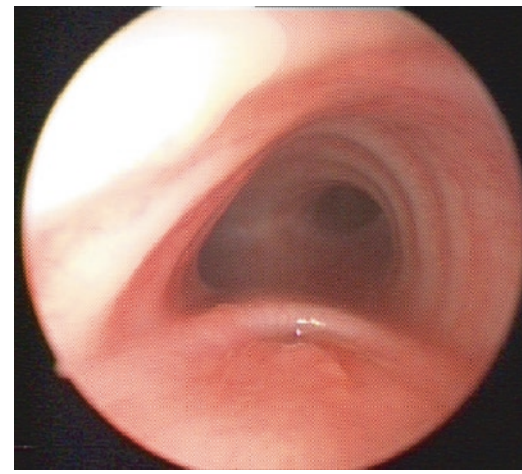

Fig. 7.7 Bronchoscopy demonstrating a posterior tracheal wall fistula just proximal to the carina

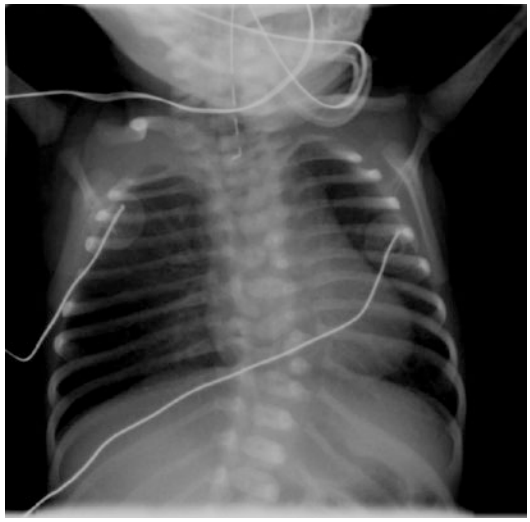

Fig. 7.8 Vertebral body malformations

rectal malformations often precedes the clinical signs and symptoms of esophageal atresia and/or tracheoesophageal fistula. In addition to physical examination, additional testing usually includes echocardiography, renal ultrasonography, spine/limb radiographs, and chromosomal analysis (Fig. 7.8).

Echocardiography, in addition to evaluating underlying cardiac defects, is used to aid in lateralizing the aortic arch which influences the surgical approach. A right-sided arch is present in 5–10 % of infants, and the esophagus and trachea are sometimes best approached on the side opposite the aortic arch [109–112]. Even at experienced centers, localization with echocardiography is only successful in two-thirds of patients [113]. Other methods to aid in the diagnosis include chest radiographs with high peak kilovoltage and air-gap magnification and localization of the descending aorta from the position of umbilical artery catheters [111, 114–116]. When a left-sided descending aorta is coupled with a right-sided arch, there is more likely an associated vascular ring completed by the ductus arteriosus [115, 117, 118]. A left thoracotomy in this circumstance allows for division of the ring, freeing the trachea, and primary esophageal repair.

More recent techniques to determine the side of the arch include computed tomography angiography (CTA) and magnetic resonance angiography (MRA). CTA permits exceptional visualization of the vascular anatomy and has the added benefit of three-dimensional reconstruction [119]. MRA offers similar cross-sectional imaging advantages to CTA, but without the risk of ionizing radiation [120]. Due to technical demands, transport requirements, and anesthesia, it is unlikely to routinely employ these methods in the clinical setting. The most satisfactory method continues to be echocardiography, which can be performed at the bedside without radiation exposure and also evaluate for significant cardiac defects.

Conclusion

Abnormal development of the esophagus and trachea may result in a wide variety of esophageal malformations ranging from pure atresia to esophageal atresia with or without tracheoesophageal fistula. There are multiple classification schemes to address both anatomic details and the infant's clinical condition. An understanding of esophageal embryology and anatomy, clinical presentation, and diagnostic approaches is essential. This knowledge will facilitate the timely arrival at the correct diagnosis, reduce associated morbidity, and allow for definitive treatment which is discussed elsewhere.

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Oesophageal Atresia Associations

8

Lewis Spitz

Approximately 50 % of infants born with an oesophageal atresia have at least one associated anomaly. It is important to perform an echocardiogram prior to surgery to correct the oesophageal anomaly in order to exclude or define the possibility of a cardiac defect. The presence of a major cardiac malformation is an important determinant of the prognosis [22]. In addition, an ultrasound scan of the kidneys will determine the presence of a renal defect.

The following table lists the incidence of associated anomalies in a single-centre (Great Ormond Street Hospital, London) [2] experience with oesophageal atresia compared with a combined analysis of almost 3,000 patients in a number of large series in the literature [4, 5, 7]:

	G.O.S.	Series
Total	47 %	47 %
No. of cases	253	2,956
Cardiovascular	29 %	22 %
Genitourinary	14 %	15 %
Gastrointestinal	27 %	21 %
Vertebral/skeletal	10 %	13 %
Respiratory	6 %	–
Genetic	4 %	4.7 %
Other	11 %	15.8 %

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Cardiovascular Anomalies [2, 7, 8]

Congenital heart anomalies are the most common associated abnormalities with oesophageal atresia and are responsible for the majority of deaths. Ventricular and atrial septal defects and patent ductus arteriosus are the most frequent cardiac defects, but tetralogy of Fallot and other complex malformations are associated with the highest mortality. Other anomalies include right-sided and double aortic arch, pulmonary stenosis, coarctation of the aorta and dextroposition.

Genitourinary Anomalies

The majority of urinary tract abnormalities are incidental findings of no clinical significance such as ureteric duplication, unilateral agenesis and horseshoe kidney. Bilateral renal agenesis (Potter's syndrome) should be excluded on ultrasound scan in an infant who fails to pass urine as treatment of the oesophageal atresia is futile. Vesico-ureterictic reflux is the most common urinary anomaly which may or may not require active treatment.

Gastrointestinal Anomalies

Anorectal malformations account for the majority of the gastrointestinal defects with equal distribution between high and low anomalies. Other

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frequent anomalies include duodenal atresia, malrotation and pyloric stenosis.

Vertebral/Skeletal Anomalies

Vertebral defects are present in around 10 % of cases and require careful long-term follow-up and management of possible scoliosis. Absent and hypoplastic radial defects, congenital dislocation of the hip and talipes equinovarus as well as rib anomalies are commonly encountered.

Genetic Defects [6]

Genetic defects account for 4 % of anomalies and include mainly trisomy 21 (Down syndrome), trisomy 18 (Edward syndrome) and trisomy13 (Patau syndrome).

Syndromes Associated with Oesophageal Atresia

VACTERL Association [9, 10, 14, 18, 25, 26]

The original VATER association was first highlighted by Quan and Smith in 1973 and expanded later to include cardiac defects in the VACTERL association – vertebral, anorectal, tracheo-oesophageal, renal and radial anomalies and limb defects. The tracheo-oesophageal component is present in 20–67 % of patients with the association, while 5–23 % of infants with oesophageal atresia have two or more components of the VACTERL association.

The incidence of the various components of the VACTERL association is as follows: vertebral/rib anomalies 67 %, anorectal defects 41 %, cardiovascular abnormalities 66 %, renal 35 % and limb defects 33 %.

The mortality for infants with oesophageal atresia within the VACTERL association is 25 %, most of which are due to complex cardiac defects.

CHARGE Association [1, 12, 13, 17, 24]

The components of the CHARGE association comprise coloboma (85 %), heart defects, choanal atresia, retarded growth and development, genital hypoplasia (almost all boys) and ear deformities. Around 2 % of infants with oesophageal atresia have this association, while of infants with the CHARGE association, 16 % have oesophageal atresia. The most frequent physical abnormalities are retarded growth (48 %) and affect the ears (90 %), eyes (90 %), heart (60 %), genitals (38 %) and choanae (35 %). Two thirds of patients are visually impaired or blind, and three quarters have hearing loss. Forty percent are on the autistic spectrum, and over 80 % are developmentally delayed, although only 10–15 % are severely retarded. A characteristic facial appearance (unusually shaped ears, unilateral facial palsy, square face, malar flattening (pinched nostrils)) is commonly observed. Semicircular canal agenesis is the major diagnostic criterion for the diagnosis of CHARGE syndrome. The mortality in this group is high, reaching up to 70 %, mostly due to major cardiac abnormalities of which the most common are tetralogy of Fallot, ventricular septal defects and right aortic arch. Mutations in CHD7, which plays a role in chromatin organisation, are responsible for this condition [28].

Potter's Syndrome

Potter's syndrome comprises renal agenesis, pulmonary hypoplasia and typical facial dysmorphia. Three quarters of infants are male. As a consequence of the renal agenesis, there is oligohydramnios and intrauterine growth retardation. The syndrome can be recognised soon after birth by the typical Potter's facies – large low set ears, prominent epicanthic folds and a flattened nose together with postural limb defects – large floppy hands and feet and deformities of the wrist and ankle joints.

Opitz G/BBB Syndrome/Schisis Association [3]

Oesophageal atresia occasionally occurs in association with omphalocele, cleft lip and/or palate and genital hypoplasia. In addition there may be hypertelorism, laryngotracheal cleft and cardiac defects with mental retardation and agenesis of the corpus callosum.

The combination of *cleft lip and palate* with oesophageal atresia has been noted to be associated with an adverse outcome. Cleft lip and palate is present in 2–3 % of cases and is associated with a mortality of 54 %, due to severe cardiac anomalies or the presence of multiple associated anomalies. Two modes of inheritance have been described in Opitz G syndrome. Mutations in the MID1 gene are responsible for the X-linked form, while the autosomal dominant form has been mapped to chromosome 22q11.2 deletion [19].

Syndromes and Associations in Which Oesophageal Atresia Sporadically Occurs

Pierre Robin Syndrome This syndrome comprises mandibular hypoplasia and glossoptosis and occasional mental retardation.

Down's Syndrome (Trisomy 21, 1 in 600–700) Recognition is based on upward slant of the eyes, prominent epicanthic folds, Brushfield spots on the iris, a flat nasal bridge, protruding tongue, short neck and flat occiput and short broad hands, single transverse palmar creases and a sandal gap between the first and second toes. Congenital cardiac defects are present in 40 % of cases.

Patau Syndrome (Trisomy 13, 1 in 7,000) These infants rarely survive 1 year. They have a small triangular head with a sloping forehead. The eyes are small with colobomata of the iris. Bilateral cleft lip and palate, cardiac defects in 80 % of cases, polydactyly and overlapping fingers and rocker-bottom feet are frequently present.

Edward Syndrome (Trisomy 18, 1 in 5,000) These infants have a prominent occiput and a disproportionately long head and small chin. The ears are low set and malformed. The mouth opening is small, and there is ptosis and wide epicanthic folds. The second finger overlaps the third. The majority have cardiac defects. Mental retardation is severe and only 10 % survive the first year.

Feingold Syndrome [14] Feingold syndrome is characterised by autosomal dominant inheritance of microcephaly and limb malformations, notably hypoplastic thumbs and clinodactyly of second and fifth fingers. Syndactyly frequently involves the second and third as well as the fourth and fifth toes. Approximately one in three Feingold syndrome patients has oesophageal or duodenal atresia or both. Anal atresia has been reported in a single case. At least 79 patients in 25 families have been reported. The syndrome has autosomal dominant inheritance with full penetrance and variable expressivity. Vertebral anomalies, cardiac malformations and deafness have been noted in a minority of patients. The syndrome is caused by mutations of the third exon of the MYCN gene [27].

DiGeorge Syndrome [11] This is a consequence of deletion of 22q11.2 and results in abnormal development of third and fourth pharyngeal pouches. Absent or hypoplastic parathyroid glands cause refractory hypocalcaemic tetany in the neonatal period. Abnormal aortic arch (right sided or double) and complex cardiac defects. Absence of thymus prevents normal differentiation of T lymphocytes resulting in neonatal sepsis. These children have characteristic facies – small chin, down-slanting palpebral fissures, protuberant ears and broad forehead. Calcium metabolism eventually corrects spontaneously and T lymphocytes mature. Prognosis depends on severity of the cardiac abnormality.

Fanconi Syndrome Hypoplastic thumb (80 %) and/or radial hypoplasia or complete absence of the radial bone, pigmented skin lesions, small

penis mental retardation in some and pancytopaenia and lymphoreticular malignancy. Genetic defects have been found in 3q, 9q or 16q locus. The pancytopaenia is characterised by hypoplasia of the erythropoietic, myeloid and megakaryocytic elements of the bone marrow and typically becomes manifest at around 8 years of age. Fourteen percent of patients with the Fanconi anaemia have gastrointestinal atresias.

Goldenhar Syndrome Preauricular skin tags and small and deformed ears, asymmetric facial hypoplasia and macrostomia, cervical vertebral defects, cardiac defects and epibulbar dermoid are the diagnostic criteria.

Smith-Lemli-Opitz Syndrome Described by Smith in 1964, this condition is characterised by microcephaly, growth and mental retardation which is generally severe, soft tissue syndactyly of the second and third toes and genital abnormality. Males predominate.

Holt-Oram Syndrome Hypoplastic thumbs (characteristically triphalangeal) and/or hypoplasia of the radius and secundum ASD/VSD. Also abnormalities of the upper limbs and shoulder girdle. Growth and development are normal.

Rogers/AEG Syndrome/Anophthalmia [15, 29] The association of anophthalmia/microphthalmia and oesophageal atresia was first described by Schenk in 1976 in a 28 mm human embryo. Since then at least 17 cases of this association have been reported. Patients with anophthalmia are usually affected bilaterally and have more severe associated anomalies of the central nervous system, craniofacial, urogenital, cardiovascular and skeletal defects. Patients with microphthalmia are generally unilaterally affected and have less severe associated anomalies. Different genes have been implicated in this syndrome including Sonic Hedgehog (shh), Pax 2 and SOX 2.

Duodenal Atresia [20, 21] Oesophageal atresia associated with duodenal atresia or more commonly with duodenal and anorectal atresia poses a specific management dilemma. The surgical decision is based on which defect is the most life-threatening. Elimination of the danger of reflux aspiration through the tracheo-oesophageal fistula would appear to be the most urgent consideration. If the infant is stable following ligation and division of the fistula, the operative procedure can continue through oesophageal anastomosis to correction of the duodenal atresia to treatment of the anorectal malformation.

Cleft Lip and Palate [16, 23] Cleft lip and palate in association with oesophageal atresia occur in 2–3 % of cases. These infants have a high incidence of associated anomalies particularly cardiac defects which account for the high mortality rate. There is also a high incidence of chromosomal anomalies such as trisomies and CHARGE syndrome. In one series, the mortality rate was over 50 %.

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Congenital Esophageal Stenosis Associated with Esophageal Atresia

9

Ashraf H.M. Ibrahim and Talal A. Al Malki

Introduction

CES is suspected by a fixed intrinsic narrowing of the esophagus present at birth and associated with congenital malformation of the esophageal wall architecture [1]. Excluding the membranous type (MD), the diagnosis of CES is only confirmed by the histologic picture [2]. The histopathologic picture may show fibromuscular disease (FMD) or tracheobronchial remnants (TBR). The latter involves ciliated pseudostratified columnar epithelium, seromucous glands, or cartilage alone or in combination [3]. The association of CES and esophageal atresia (EA) and/or tracheoesophageal fistula (TEF) ranges from 0.4 % [1] to 14 % [4–6]. The authors believe that this association is common and that many cases are over looked. CES has been most frequently associated with EA with distal TEF (64 %), followed by isolated TEF (20 %) and isolated EA (16 %) [7]. In the authors experience, the incidence of CES being associated with pure atresia is higher than in EA and distal TEF (50 % vs 11.3 %) [6].

The first case of CES associated with an EA was reported from the Montreal Children Hospital by Dunbar in 1958 [8]. This was followed by 34 reports in the literature till 2008 [1, 4–7, 9–37]. Reviewing the histologic structure and the etiology of esophageal dysmotility in this association is mandatory for understanding this topic.

Histology of the Atretic Esophagus

Few reports are available in the literature regarding the histology of the atretic esophagus. Hokama et al. in 1986 [3] examined six autopsy unoperated cases of EA and TEF and also two surgical specimens. They defined the lower segment of the esophagus as that part where the wall is arranged into four normal layers: mucosa, submucosa, muscularis externa with myenteric plexus, and adventitia. The fistula was defined as that portion between the tracheal/bronchial connection and the transition to esophagus with normal layers. Tracheobronchial elements were defined as ciliated pseudostratified columnar epithelium, seromucous glands (as opposed to normal esophageal mucus glands), or cartilage, alone or in combination. Hokama et al. found a high incidence of TBR in the lower esophagus (five autopsy cases out of six and in the two surgical specimens). They concluded that TBR may be very common in EA/TEF that may lead to stenosis and abnormal motility after successful

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anastomosis. They also proposed that lack of a normal muscle coat at the fistulous end may cause esophageal dysmotility. They questioned the feasibility of including the fistula in the anastomosis should this correlation be confirmed.

In 1997, Merei et al. [38] from Australia carried out a histologic study of EA and TEF in an adriamycin animal model. They found that all the fistulae were lined with ciliated respiratory epithelium extending to a variable distances from the origin and in some instances as far as the stomach. Cartilage was occasionally seen in the wall. Transition from ciliated epithelium to stratified squamous epithelium occurred either by partial or abrupt replacement. The muscle layer was absent at the fistulous origin. Later, it was composed of irregular smooth muscle fibers that were not properly arranged into normal esophageal layers. After transition to normal esophageal epithelium, it became regular.

Dutta et al. in 2000 [39] reported a histological study of EA/TEF in 65 cases. The lining epithelium was stratified squamous in 36 cases, pseudostratified squamous in 2, and not seen in 27 cases. The mucous glands were abnormally high in number in 23 cases and with abnormal mucin secretion (typical of respiratory glands) in 23 cases. The ducts were dilated in six cases but with increased number in four. Cartilage was seen in eight cases with large number of mucous and seromucous glands also with abnormal mucin secretion. The muscularis propria was poorly oriented in 17 cases, well developed in 17, and disorganized in 13. Out of the studied cases, one autopsy case showed cartilage with mucous and seromucous glands. In another autopsy case, only mucous and seromucous glands were seen without cartilage. Both autopsy cases showed abnormal mucin secretion. The authors proposed that the TBR in the repaired esophagus as well as a disorganized muscle coat may be part of the transition from the fistula to a normal esophagus. The extent of this TBR is variable, and it may be premature to suggest this as a cause for esophageal dysmotility in each case. The authors stressed the point that loss of normal esophageal function may be due to abnormal numbers of glands and ducts and presence of abnormal mucin production. TBR may present with esophageal stricture refractory to dilatations but have dramatic response to resection. They claimed that these strictures are present only in the lower esophagus away from the area of anastomosis. However, this statement has been challenged. CES should be considered in the etiology of anastomotic stricture [6]. In our series, surgical specimens for histopathologic studies were obtained from the tip of the lower esophageal pouch during primary repair of EA/TEF cases [6]. Up to date, 10 patients out of 65 (15.4%) had histologic pictures suggestive of CES. None of the patients studied had absent muscle layers. This excludes using the fistula in the anastomosis. Two cases had fibromuscular disease (FMD), five with tracheobronchial remnants (TBR) without cartilage, and three with cartilage. The epithelium for these ten patients was normal in seven patients and pseudostratified columnar ciliated in three. These three cases showed increased numbers of mixed respiratory glands, ducts, and cartilage that extended from the submucosa to the adventitia causing muscle distortion (Fig. 9.1). One case with pure EA and gastric pull up showed TBR involving the whole lower esophageal pouch down to the cardia. Five patients showed mixed respiratory glands without cartilage that extended from the submucosa to the adventitia causing muscle distortion (Fig. 9.2). The glands were considered abnormal if they are seromucous or mucous glands that are increased in number and/or abnormally located outside the submucosa. The remaining two cases showed muscular hypertrophy and extensive fibrosis consistent with FMD (Figs. 9.3 and 9.4).

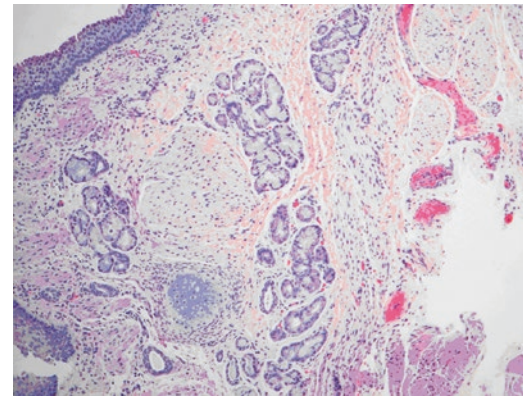

Fig. 9.1 Tracheobronchial remnants represented by pseudostratified columnar ciliated epithelium together with seromucous glands and cartilage (case 10)

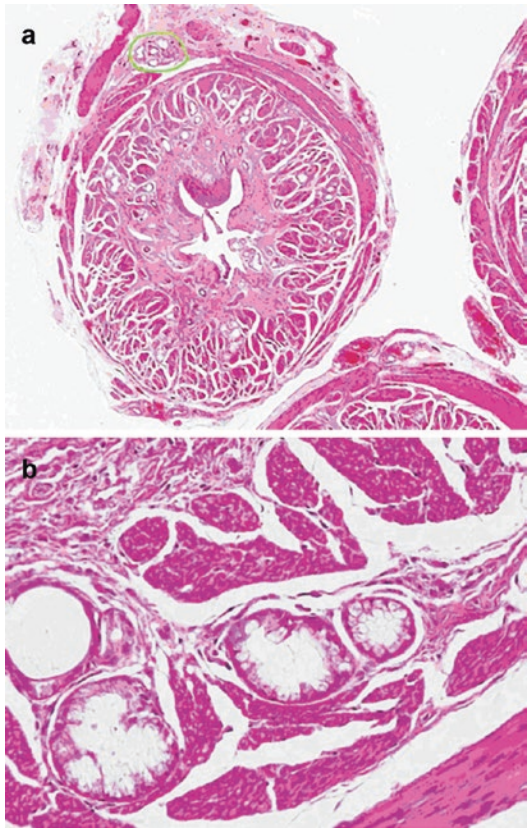

Fig. 9.2 (**a**) Mixed respiratory glands extending from the submucosa to the adventitia of the esophagus causing muscle disruption. (**b**) A magnified photograph of **a.** For the same patient

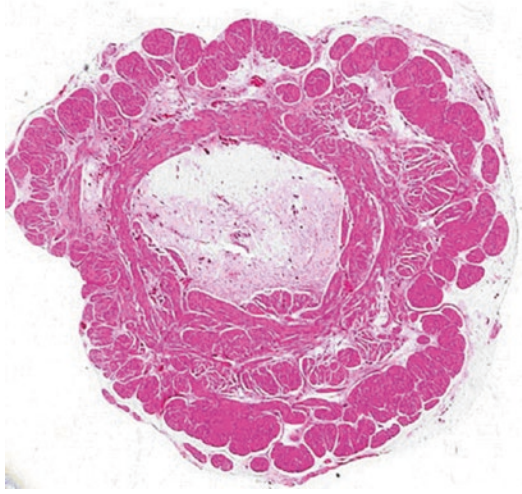

Fig. 9.3 Hypertrophic muscle fibers together with fibrosis

Etiology of Esophageal Motility Disorders in Esophageal Atresia

The etiology of esophageal dysfunction in cases of CES after repair of EA is not understood. It may be due to either CES or EA alone or in combination. *An acquired origin* for esophageal dysmotility is proposed. Extensive mobilization and denervation of the esophageal segments could aggravate reflux and motility disorders [40]. Normal peristaltic activity was documented preoperatively in the proximal esophagus in two patients who had EA without a fistula. One patient examined postoperatively showed a disturbed motility pattern [41]. Vagal damage may be the cause of motility dysfunction [42]. Extensive pouch mobilization is associated with severe motor disability [43].

A congenital origin for esophageal motility disorders after EA repair was proposed. Romeo et al. in 1987 [44] has documented disturbed motility preoperatively in patients with EA. Furthermore, motility disorder has been documented in patients having isolated TEF without EA [45]. Transection and anastomosis of the esophagus did not cause motility disorders [46]. Few histological studies have been conducted in the literature to document the congenital origin of esophageal dysmotility after successful repair of EA. Most of these studies have been done on autopsy patients [3, 47] or animal models [38, 48, 49]. Abnormal Auerbach's plexus was found in the esophagus and stomach in five autopsy patients with EA and TEF. The plexus was looser than normal in the distal esophagus and to a lesser extent in the proximal esophagus and stomach fundus. The ganglia were larger than normal. The smooth muscle layers were documented to be normal [47]. In other studies [3, 6, 38, 39], tracheobronchial elements, namely, ciliated pseudostratified columnar epithelium and seromucous glands with or without cartilage together with irregular smooth muscle fibers, were seen in sections of the distal esophagus. Seromucous glands were seen among muscle bundles of the lower esophageal pouch. Abnormal mucus glands causing muscle distortion were also documented. The transition from the fistula

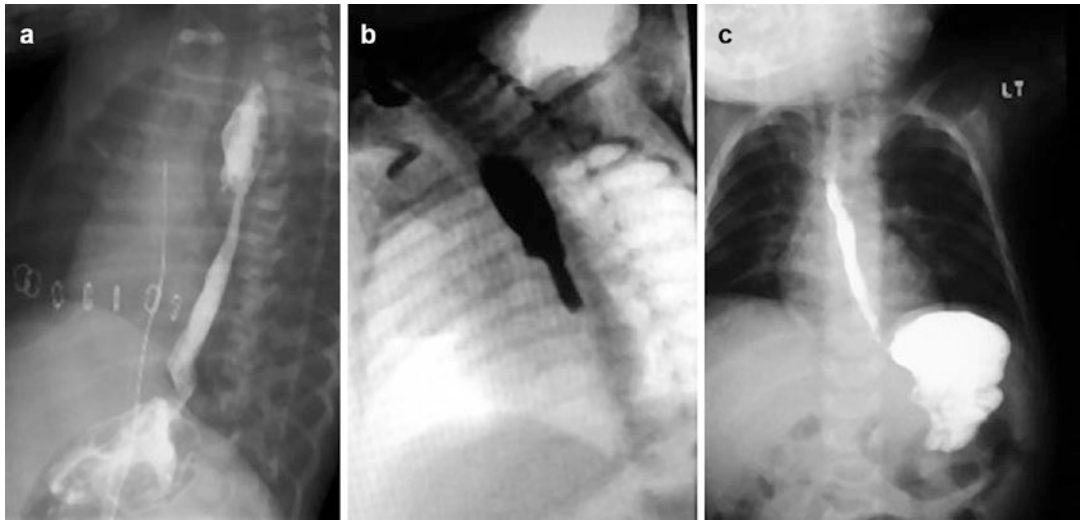

Fig. 9.4 Case 10 showing: (**a**) Initial normal barium swallow and meal. (**b**) Photo from videofluoroscopy with major dysmotility after 1 month with failure of passage of the contrast distally for more than 5 min. (**c**) Barium swallow and meal after fundoplication and lower esophageal myectomy showing improvement of motility

to normal esophageal histology takes place at a variable distance from the origin of the fistula and may extend down to the cardiac end [3, 6, 38]. Surgical specimen from the tip of the lower pouch also showed a histologic picture consistent with FMD [6].

Singarm et al. in 1995 [50] examined the histological and immunohistochemical features of CES of the FMD in two adults. In comparison to three controls, CES esophagi showed infiltration of neutrophils in the myenteric plane without any increase in collagen. NADPH diaphorase histochemistry showed a significant reduction of myenteric nitrinergic neurons and fibers of the circular muscle. The specific total lack of nitric oxide (NO) inhibitory innervation may be an important mechanism in the pathogenesis of stenosis and aperistalsis of the esophagus in this disorder.

Neuropeptides are abnormal in the atretic esophagus in the Adriamycin fetal rat model [48, 49] and in humans [51–53]. The density of the nerve plexus, ganglia, and number of cell bodies per ganglia immunostained by neuron-specific enolase (NSE), vasoactive intestinal peptide (VIP), or substance P (SP) was significantly reduced in EA/TEF fetuses. So, there are significant abnormalities of the intramural nervous components of the esophagus in EA/TEF fetal rats, involving both the excitatory (SP-labeled) and inhibitory (VIP-labeled) intramural nerves which may be the cause of esophageal dysmotility in EA/TEF [49].

The circumferential neuronal distribution in the myenteric plexus in the atretic esophagus of the rat model was reduced by 50%. The near-complete ring of nerve tissue along the plane of the myenteric plexus was replaced by clusters of nerve tissue in the atretic esophagus. This abnormal distribution of nerve tissue in the atretic esophagus may be contributing factor in the esophageal dysmotility seen in EA [54]. Qi et al. using the same model showed that the vagus nerve gave rise to fewer branches in the esophagus and assumed abnormal route at the level of the lower esophagus [55]. Boleken et al. examined the distal end of the proximal esophageal atretic segment of neonates undergoing EA/TEF repair for intrinsic neuronal innervation. They found that the distribution of ganglion cells and some nerve fibers is deficient. The inadequate and abnormal neuronal innervation of the esophagus could be related to esophageal dysmotility in EA. Deficient expression of glial cell line-derived neurotrophic factor (GDNF) could have an important role in the defective and/or abnor-

mal neuronal innervation of the atretic esophageal segment [51]. Similarly, Li Kai et al. in 2007 investigated the structural characteristics and the expression of a group of neuropeptides in the specimens obtained from the fistulous end of the lower esophagus of patients with EA/TEF. They found imbalance of neurotransmitters excretion in nerve vesicles, abnormal intrinsic dysplasia of nerve plexus, and increased expression of certain neuropeptides, e.g., VIP and nitric oxide synthase (NOS) were the main characteristics of the esophagus with abnormal intrinsic innervation, which may be responsible for postoperative esophageal dysfunction [52]. Most recently, Pederiva et al. examined the intrinsic esophageal innervation in children with isolated EA using specimens from the proximal and distal esophageal segments. There were denser fibrilar network and larger ganglia than controls [53].

Kawahara et al. in 2003 [56] investigated the motor function in four cases with isolated CES. Esophagogram showed stasis of contrast proximal to esophageal narrowing in two cases with FMD and one case with TBR. Three patients showed pathologic acid exposure by pH monitoring despite absence of evidence of esophagitis by endoscopy. Manometry showed synchronous esophageal contractions in FMD and TBR cases. LES pressure was at least 20 mmHg. Swallow-induced LES relaxation was incomplete in these cases. The authors concluded that gastroesophageal reflux (GER) and impaired esophageal motility are common in CES with FMD and TBR. Synchronous contractions seen in patients with FMD and TBR could be related to abnormal innervation of NO. The manometric data in CES in children reported by the Pittsburgh group showed segmental aperistaltic zone at the level of stenosis with local decreased pliability. The superior and inferior sphincters responded normally to swallowing [57]. A manometric study in 12 cases of CES showed another high-pressure zone (HPZ) in addition to the lower esophageal sphincter (LES) found in nine of the patients. This additional pressure zone disappeared after treatment [58]. Cheng in 2004 reported a case of achalasia-like esophageal dysmotility in a 14-year-old boy after successful repair of EA/TEF in the neonatal period. This was proved by clinical, radiological, and manometric study. The manometric features were a cardiac sphincter of 2 cm in length with a high pressure above 40 mmHg with aperistalsis in the esophageal body and failure of the cardiac sphincter to relax after a swallow. The condition responded well to Heller myotomy [59].

Kawahara in 2004 [60] reported the usefulness of videomanometry for studying pediatric esophageal motor disease in four postoperative cases of EA/TEF and one case of isolated distal CES due to TBR. These cases frequently showed impaired esophageal transit during defective esophageal peristaltic contractions. Videofluoroscopic image in cases of EA showed marked stasis of contrast in the esophageal body. Manometry showed absent contractions in the middle esophagus. The distal esophagus showed low-amplitude peristaltic contractions in two cases, low-amplitude synchronous contractions in one case, and no contractions in one case. The authors concluded that impaired esophageal transit was caused by defective luminal closure especially in the middle esophagus during deglutition, but not by LES malfunction. Videofluoroscopy of the case of CES showed stasis of the contrast in the distal dilated esophagus associated with narrowing at the end of the esophagus mimicking achalasia. Manometry showed swallow-induced LES relaxation and low-amplitude synchronous contractions in the whole esophageal body.

Types of Congenital Esophageal Stenosis

Fekete et al. [1] defined CES as intrinsic stenosis caused by congenital malformation of the esophageal wall. It involves a type with TBR, another with segmental hypertrophy of the muscularis and diffuse fibrosis of the submucosa (FMD), and a third type with a membranous diaphragm (MD). The most common type of CES was that of the TBR variety (75 %) followed by the FMD (25 %) [4, 6]. These percentages might not be correct. The FMD responds better to balloon dilatation. If dilatation is successful, no specimen is available. So, a definitive subtype cannot be

determined. Also the percentage of each type that will respond to dilatation is not known [34]. The MD type is rarely reported in association with EA/TEF [9, 32, 61]. It is possible that CES can be multiple [62]. The stenotic area may involve the perianastomotic area or even may extend distally to a variable distance [4, 6]. For this reason, we disagree with the statement that CES does not involve the anastomotic site and is always separate from it [1, 35]. However, a distal isolated area of CES separate from the anastomotic site may be present [4, 5, 7, 15]. All the 11 cases reported by Kawahara in 2001 were found to have narrowing between the anastomosis and the gastroesophageal junction: in the mid-esophagus in two and in the lower esophagus in nine patients [4]. In our experience with ten cases, only one of them had distal esophageal stricture due to FMD that required resection. So, in our series, CES is more common at the perianastomotic area (Tables 9.1, 9.2, and 9.3).

Diagnosis

A high index of suspicion should be raised in all cases of EA. CES is an intrinsic stenosis that may be present at birth but not necessarily symptomatic [7]. The diagnosis of CES is suspected in a neonate with EA if a size 8 French nasogastric tube cannot be passed into the stomach [4, 7]. However, passage of the tube down to the stomach does not rule out CES [7]. The diagnosis of CES before or during primary repair of EA is possible; however, simultaneous repair of the stenosis by doing a double esophageal anastomosis is a controversial approach [4, 32]. An esophagogram demonstrating a narrow segment above the cardia is radiologically diagnostic for CES when found in the neonatal period [7, 63]. Minor esophageal dysmotility as detected by barium is defined as aperistalsis, antiperistalsis, and simultaneous or uncoordinated contractions. The dysmotility is considered major if the transit time for

Table 9.1 Group I (two cases with FMD)

Criteria	Case 1: EA/TEF	Case 2: EA/TEF
Sex	Female	Female
GA/BW	33 weeks/1.9 kg	37 weeks/2.9 kg
Histopathology[a]	Unremarkable	FMD
Initial barium	No dysmotility, GER++, no stricture	No dysmotility, GER ++, no anastomotic stricture
Early postoperative period	Uneventful	Uneventful
Onset of symptoms	3 months, mainly dysphagia, aspiration, and FTT	2 months, mainly dysphagia, aspiration, and FTT
Subsequent barium	Anastomotic stricture extending distally	Anastomotic stricture
	GER +++	GER +++
	Major lower esophageal dysmotility	Minor dysmotility
Esophagoscopy	Normal mucosa	2nd degree esophagitis
Action	Failed antireflux medical treatment and dilatation	Failed medical antireflux measures and frequent dilatation
	Failed myotomy/Nissen fundoplication with gastrostomy at 6 months	Nissen fundoplication at 6 months
	Resection of distal stenotic area at 9 months showed FMD	Esophageal diverticulectomy at 14 months
		Required 4 dilatations
Outcome	Improved	Improved
Follow-up period	12 years	10 years

GA gestational age, *BW* birth weight, *FTT* failure to thrive
[a]Histopathology = surgical specimen from the tip of L.P at primary or delayed primary repair

Table 9.2 Group II (five cases). TBR without cartilage

Criteria	Cases 3, 4, and 5: EA/TEF	Case 6: pure EA (delayed repair at 5 months)	Case 7: EA/TEF
Sex	Female	Female	Female
	Male		
	Female		
GA/BW	33 weeks/1.8 kg	37 weeks/2.4 kg	37 weeks/2.5 kg
	37 weeks/2.4 kg		
	35 weeks/1.7 kg		
Histopathology	TBR/no cartilage	TBR/no cartilage	Operated somewhere else/no pathology specimen
Initial barium	No dysmotility in one, minor dysmotility in 2, GER ++ in all, slight stricture in all	Minor dysmotility	Minor dysmotility
		GER ++	GER ++
		No stricture	No stricture
Early postoperative period	Uneventful	Uneventful	Uneventful
Onset of symptoms	2 months, mainly slow feeding and occasional aspiration	10 months mainly dysphagia, FTT, and recurrent aspiration	3 months, dysphagia, aspiration, FTT
Subsequent barium	Isolated anastomotic stricture	No stricture	Stricture +++
	Minor dysmotility	Minor dysmotility	Minor dysmotility
	GER +++	GER +++	GER ++
Esophagoscopy	Norma mucosa in all	2nd degree esophagitis	Normal
Action	Medical antireflux measures and dilatation	Medical antireflux measures failed Thal's fundoplication and temporary gastrostomy	Failed medical antireflux measures Frequent dilatations failed Thal's/gastrostomy Failed dilatation Anastomotic resection → TBR without cartilage
Follow-up period/ outcome	5–9 years	7 years	3 years
	Improved	Improved	Improved

the bolus to go to the stomach is greater than 5 min [6]. The problem of major dysmotility is that it develops late and can be fatal or amenable to major complications.

Taking a surgical specimen routinely from the tip of the lower pouch during primary repair of EA may show a histological picture consistent with FMD or TBR [6]. This mandates close observation. The latest case in our series (case 10) showed TBR with cartilage (Fig. 9.1). The initial esophagogram was normal. A repeat fluoroscopic esophagogram 1 month later showed major esophageal dysmotility due to aperistalsis in the perianastomotic area. The patient required a feeding gastrostomy, anterior partial fundoplication, and lower esophageal anterior myectomy. The major esophageal dysmotility as seen at fluoroscopy improved, and partial oral feeding was allowed. The histology of the myectomy was normal. We learn from this case that the histologic picture confirmed the site and type of CES. The forthcoming scenario was anticipated. Dysphagia which developed after 1 month was not due to introduction of solid food but was due to pure dysmotility which preceded mechanical stricture. The lower esophageal myectomy helped to improve major dysmotility probably due to a decrease in the pressure of the lower high-pressure zone.

The late-onset diagnosis is suspected by the clinical triad of recurrent aspiration, dysphagia, and FTT together with the aid of an esophago-

Table 9.3 Group III. TBR with cartilage (three cases)

Criteria	Case 8: EA/TEF	Case 9: pure EA	Case 10: EA/TEF
Sex	Female	Male	Male
GA/BW	30 weeks/1.3 kg	35 weeks/2 kg	37/2.5 kg
Histopathology	TBR with cartilage	TBR with cartilage	TBR with cartilage
Initial barium	Minor dysmotility, GER ++ Slight anastomotic stricture	–	Normal
Early post-operative period	Uneventful	–	Uneventful
Onset of symptoms	3 months, dysphagia, aspiration and FTT	–	One month/slow feeding
Subsequent barium	Stricture at anastomotic site extending distally Late major dysmotility GER ++++	–	Major esophageal dysmotility at 1 month No GER
Esophagoscopy	Scope could not pass	–	–
Action	Medical antireflux measures and dilatations failed Thal's fundoplication and gastrostomy at 6 months Recurrent symptoms Resection of anastomotic stricture at 1 year. *Histopathology*: TBR with cartilage Recurrent stricture Frequent dilatations	Failed delayed primary repair Required resection of the whole lower esophagus and gastric pull-up *Histopathology* showed TBR with cartilage extending from the tip down to cardiac end of the lower esophagus	Thal's fundoplication Gastrostomy at 6 weeks Lower esophageal myectomy showed normal histology Partial oral feeding and gastrostomy
Follow-up/outcome	Improved now 6 years old		Improved now 9 months old

gram [64]. Patients may present with distal esophageal foreign bodies [7]. A barium study is the diagnostic and follow-up tool. Full cooperation between the radiologist and the surgeon is required.

The presence of GER in cases of EA with CES is said to be unlikely [27]. However, others believe that it is common [4–6]. Esophagoscopy and biopsy, pH monitoring, and possibly manometry may be required [58]. However, even with these investigations, it may be difficult to differentiate between CES and stricture due to GER [7]. Errors in diagnosis are common as most of these patients are diagnosed and managed as peptic stricture [5, 7].

Precise preoperative diagnosis of CES is important. The type of stenosis determines the modality of treatment. Without the preliminary histologic picture, the preoperative differentiation between FMD and TBR with cartilage is difficult. In a review of the literature for 59 cases with TBR with cartilage up to 2004, a correct preoperative diagnosis of the underlying etiology of stenosis was not reached in most cases. The majority were diagnosed as achalasia or peptic stricture [64]. Esophagoscopy and biopsy may fail to show deep-seated ectopic tissue [1, 65]. Fluoroscopy may show abrupt narrowing in cases of TBR, while that of the FMD may show more gradual, regular, and well-centered narrowing. However, fluoroscopy does not always show these typical findings [35]. During balloon dilatation, the presence of a short, sharp waist-like impression which suddenly disappears with increased pressure means the presence of cartilaginous rings [7, 34]. Endoscopic ultrasonography is said to be useful to distinguish TBR with cartilage from FMD [35, 66, 67]. Intraoperative palpation and the use of the flexible esophagoscopy may be of help [35, 65]. The author like others [58] found that intraoperative palpation of the lesion is not always easy. However, these modali-

ties suspect but not confirm the presence and the type of CES. The diagnosis is only confirmed by the histologic picture.

Treatment

Cases of EA diagnosed or suspected to have associated CES in the neonatal period should have utmost attention. A normal early fluoroscopic barium swallow and meal does not exclude CES and must be repeated at 4–6 weeks. The development of the triad of esophageal dysmotility, GER, and stricture should be managed as early as possible. By doing this, the consequences of malnutrition, recurrent aspiration, and even mortality can be avoided. Full antireflux measures and balloon dilatation for stricture should be initiated. If the dysmotility is major, a partial anterior wrap together with a feeding gastrostomy is indicated. During the procedure, a myectomy as long as possible of the lengthened lower esophagus is taken and sent for histopathologic and possibly histochemical examination.

For those cases discovered late, proper chest treatment, antireflux measures, and nutritional support should be started. Antireflux measures together with balloon dilatation should be the initial treatment of all forms of CES associated with EA [7, 34].

Most cases with TBR without cartilage respond well to medical antireflux measures together with balloon dilatations. Three out of four patients in our series showed excellent long-term clinical outcome despite the persistence of radiological minor dysmotility. Only one patient required surgical resection after failed balloon dilatations. Histopathology of the resected specimen showed glands without cartilage.

Cases with TBR with cartilage will require a limited surgical resection and primary anastomosis if balloon dilatations failed on three occasions [4, 5, 7, 35]. Surgical resection will also be indicated if initial sufficient dilatation is not achieved or symptoms recur very soon after dilatation [58]. Unnecessary prolonged trials of balloon dilatations should be avoided because the trials will be unsuccessful [64]. Some authors experienced severe complications with repeated dilatations [4, 68, 69]. The extent of TBR into the distal esophagus should be accurately assessed during surgery. A frozen section biopsy may be required. A fundoplication is recommended after resection if it disturbs the gastroesophageal junction and to avoid the possible postoperative complications of GER and hiatus hernia [1, 7, 33]. Circular myectomy was performed successfully for the treatment of CES due to TBR [70, 71]. Thoracoscopic resection of a distal CES and esophageal end to end anastomosis was successfully performed [72]. Very recently, a laparoscopic lower esophageal stricturoplasty with anterior fundoplication for CES due to TBR was also successful [73]. Surgical resection may be complicated by recurrent anastomotic stricture that may require few postoperative dilatations.

Cases with FMD usually respond to balloon dilatations [4, 7, 35]. Longitudinal myotomy with Nissen fundoplication may be curative [4, 35]. A limited surgical resection may be required if the above measures fail [4, 35, 58].

Cases of MD and multiple stenoses can be treated with esophageal dilatations alone. Endoscopic partial resection of the membrane can be done at the time of dilatation [35].

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Choanal Atresia, Esophageal Atresia, Facial Anomalies, and Dysautonomia

10

Francesco Cozzi and Denis A. Cozzi

Introduction

The old concept that during the neonatal period bilateral choanal atresia causes life-threatening apnea whereas unilateral choanal atresia causes only a unilateral nasal discharge is still well accepted. The cause of life-threatening apnea is considered the inability to open the mouth. The ensuing cyanosis stimulates crying, which is a method to induce mouth breathing, thus relieving the obstructive apnea. As the relief comes, the infant ceases to cry and closes his or her mouth. After a few seconds, the respiratory problems come again [1]. The constant repetition of this cycle is yet described as the main clinical manifestation of bilateral choanal atresia, whereas a persistent nasal mucoid discharge from the affected side is described as the main clinical manifestation of unilateral choanal atresia [54].

In 1977, the senior author reported clinical observations and respiratory studies suggesting that the life-threatening apnea of infants with choanal atresia or choanal stenosis was not due to an inability to switch from nasal to oral ventilation, but it was due to an inability to sustain an adequate oral ventilation. The pathogenic mechanism of oropharyngeal airway obstruction appeared quite similar to that described as glossoptosis by Pierre Robin in infants with micrognathia or in infants with hypertrophied adenoids, that is, a posterior displacement of the tongue obstructing the upper airways [3]. In the senior author's paper, it was also speculated that glossoptotic upper airway obstruction could play a role into the pathogenesis of apparent life-threatening episode (ALTE) observed in some infants with esophageal atresia and into the pathogenesis of asphyxial death in some victims of sudden infant death syndrome (SIDS) [10].

With an increasing number of clinical observations, it became clear that infants with either bilateral or unilateral choanal atresia/stenosis (CA) or with esophageal atresia (EA) present also a common clinical picture [14, 35, 37]. Actually, the respiratory problems, referred to a development delay of respiratory control, were often associated with other clinical manifestations of autonomic disorders. A possible explanation of these findings was that the face, the esophagus, and the autonomic nervous system have a common origin from the cephalic neural crest. Therefore, a cephalic neurocristopathy, that is a maldevelopment of cephalic neural crest derivatives [9], may explain why both CA and EA can be associated with symptoms and signs of autonomic dysfunctions. Support to this theory comes from the presence in infants with CA or EA of similar facial dysmorphisms, which are considered markers of a cephalic neurocristopathy [39].

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This is a review of our main contributions to the literature during more than three decades regarding the clinical and pathophysiological manifestations that the infants with EA share with those with CA.

Pathophysiology

Early respiratory studies in infants with bilateral choanal atresia suggested that the main pathogenic factor of upper airway obstruction was a backward aspiration of the tongue. Flow signals were obtained from a pneumotachograph connected to tight-fitting mask. Esophageal pressure, as an index of intrapleural pressure, was measured with a water-filled polyethylene catheter passed through the mouth into the lower esophagus and connected to a pressure transducer. Infants with CA were breathing through an oropharyngeal cannula without respiratory distress. When the oropharyngeal cannula was removed, increasing esophageal pressure swings with very negative values, and a complete absence of airflow occurred (obstructive apnea, equivalent of Muller's maneuver). The conclusion was that the strong negative pressure generated by the inspiratory efforts was responsible for the aspiration of the tongue and the consequent oropharyngeal obstruction [10]. Therefore, we proposed the term vacuum-glossoptosis to indicate that falling back of the tongue was not due to a simple mechanical consequence of a short mandible, as proposed by Pierre Robin [3], but was mainly due to aspiration of the tongue and its sealing to the palate [25].

Subsequent clinical observations showed that some infants with EA or CA [37], as well as some infants with Pierre Robin syndrome without micrognathia, or some infants with unilateral choanal atresia, or some infants with a nasal obstruction caused by a simple rhinitis [14] may present recurrent episodes of glossoptosis-apnea. The absence of correlation between the severity of symptoms and the degree of anatomical or inflammatory upper airway obstruction suggested that also the muscular activity of the genioglossus plays an important role in maintaining the patency of the upper airways [14]. The tongue and the soft palate act as a dynamic flap valve that may easily obstruct the oropharyngeal airway when the negative inspiratory pressure overcomes the genioglossus forces, which tend to protrude and depress the tongue [24].

During normal breathing, there is an activation of genioglossus and of other upper airway-dilating muscles prior the activation of the diaphragm and of other inspiratory muscles [27, 29]. This pre-activation serves to counteract the negative intrathoracic pressure generated by the inspiratory muscles, thus avoiding the aspiration of the tongue and the collapse of the musculomembranous walls of the pharynx. During loaded breathing, animal experiments have demonstrated the presence of a powerful reflex mechanism to protect pharyngeal patency. Any increase in resistance in the upper airway is followed by an increase in negative pressure during inspiration, resulting in stimulation of laryngeal mechanoreceptors. This afferent feedback to central pattern generator in the brainstem determines respiratory stimuli to activate the genioglossus [27, 29].

The concept that glossoptosis-apnea was the result of an abnormal control of respiration was further supported by the frequent presence in infants with both CA and EA of obstructive and central hypopneas/apneas [37]. Obstructive apnea implies an inspiratory effort not associated with pre-activation of upper airway-dilating muscles. Central hypopnea/apnea implies a decreased or absent stimulus from the respiratory centers to the inspiratory muscles (Fig. 10.1). In addition, in some patients with glossoptosis-apnea syndrome, many symptoms were not relieved by the surgical removal of the anatomic obstruction, suggesting persistence of a dysfunction of upper airway-dilating muscles [35]. A similar persistence of some clinical manifestations following adenoidectomy was long before noticed and called "adenoidism without adenoids" or "glossoptism" [3, 4]. The persistent symptoms disappeared spontaneously at long-term follow-up, thus indicating that they were not caused by an anatomical obstruction

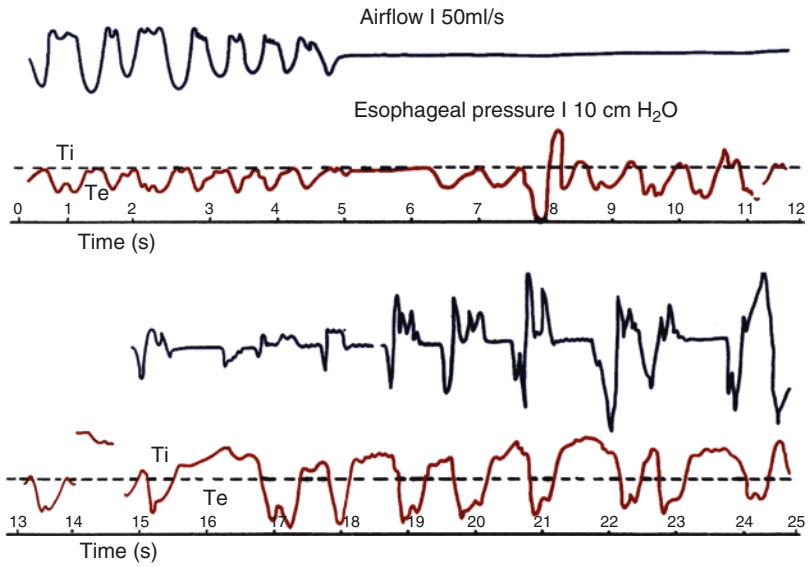

Fig. 10.1 Central hypopnea/apnea followed by obstructive apnea in an infant with esophageal atresia and distal tracheoesophageal fistula. Note: (1) parallel reduction followed by complete absence of airflow and esophageal pressure, that is central hypopnea/apnea (0–6 s); (2) inspiratory effort without airflow, that is obstructive apnea (6–13 s); (3) grunting expiration, characterized by prolonged expiratory time, interrupted expiratory flow despite positive expiratory pressure, and progressive increase of retarded expiratory flow (*arrows*) (14–3 s). Ti and Te are inspiratory and expiratory time, respectively

but were related to a "maturational dysautonomia" [35].

The main conclusion was that various types of upper airway anatomical obstructions, including CA, EA, congenital micrognathia, or even a simple upper respiratory tract infection, become symptomatic if associated with an impaired reflex activation of upper airway-dilating muscles. The infant who is not able to counterbalance the increased inspiratory pressure brought about by the anatomical or inflammatory obstruction presents recurrent episodes of functional upper airway obstruction [35, 37].

Clinical and radiologic studies in infants with various types of obstructions of the nasal airway showed that the respiratory distress is characterized by signs of an obstruction of both inspiration and expiration [2, 6, 22, 26]. In infants with CA, the mechanism of the obstruction in expiration is considered the anatomical obstruction of nasal airway due to choanal atresia associated with the functional obstruction of oral airway due to the sealing of the soft palate to the base of the tongue [6, 22]. In infants with EA, expiratory airway obstruction is conventionally attributed to tracheomalacia. However, our studies of pulmonary mechanics and breathing patterns during glossoptosis in infants with CA or in infants with EA have shown that the expiratory obstruction is characterized by an absent flow despite a positive expiratory pressure and a retarded expiratory flow pattern (Fig. 10.1) [42]. The obstructed expiratory efforts (equivalent of the Valsalva maneuver) and the retarded expiratory flow were associated with an audible grunting, which was loudest over the neck. Therefore, the expiratory airways obstruction may be referred, at least in part, to active braking of the expiratory flow, that is, an active closure of the glottis associated with a positive expiratory pressure. This expiratory flow pattern is frequently found in babies with hyaline membranes [17] or even in normal babies with a subclinical grunting [19]. Forced expiration is a breathing strategy that serves to defend lung volume and lower airway patency by forcing gas retrogradely into the peripheral airways during expiration.

In conclusion, infants with various types of upper airway obstruction present respiratory problems if the anatomical or inflammatory obstruction is associated with an upper airway instability responsible for a functional glossoptotic pharyngeal obstruction. Recurrent episodes of functional upper airway obstruction may bring about a low lung volume, that is, a lower airway instability. In this condition, active braking of the expiratory flow is a useful breathing strategy to avoid collapse of widespread areas of the lung and the consequent intrapulmonary right-to-left shunt. This breathing strategy is particularly useful in infancy since large intrapulmonary right-to- left shunt seems to play an important role into the pathogenesis of ALTE and SIDS [14, 35–37, 39, 41, 46].

Table 10.1 Prevalence of main clinical features in infants with choanal atresia/stenosis and infants with esophageal atresia

	Esophageal atresia (%)	Choanal atresia (%)
Respiratory problems		
Inspiratory dyspnea	88.7	98.2
Expiratory dyspnea	43.7	49.2
ALTE	35.0	29.8
Sudden death	3.7	3.5
Feeding problems		
Oropharyngeal dysphagia	62.7	57.8
Vomiting/GER	60.4	52.6
Failure to thrive	45.0	40.0
Bradycardia	25.0	12.2
Hyperthermia	16.2	21.0
Sialorrhea	18.6	17.5
Hyperhydrosis	34.8	22.8

Clinical Features

Nearly all symptomatic infants with CA or EA have one or more clinical manifestations of dysautonomia [35, 37, 39] (Table 10.1).

The most frequent clinical manifestation is the presence of respiratory symptoms and signs, usually observed during the first months of life. These problems are triggered by any respiratory load including upper respiratory tract infections, crying, exercise, supine position, and flexion of the neck. The respiratory problems are also precipitated by those factors which decrease the activity of upper airway-dilating muscles including sleeping, sedatives, and anesthesia.

The clinical manifestations of respiratory problems have been described in details both in infants with EA [5, 15, 37, 39] and in infants with CA [14, 35]. All patients with respiratory distress have one or more signs of inspiratory obstruction, including snoring; sniffing; stridor; head retraction; open mouth breathing; glossoptosis; retrognathia; indrawing of the cheeks, lip, and soft tissues of the neck; indrawing of the sternum (paradox respiration); and reduced or absent air entry. Open mouth breathing is a maneuver adopted to bring the tongue forward, thus preventing glossoptotic pharyngeal obstruction [3, 23]. Similarly, head extension (opisthotonous) is a protective maneuver to prevent glossoptotic pharyngeal obstruction by increasing the pharyngeal dimensions [30, 38].

The signs of inspiratory obstruction do not reflect an increased alveolar resistance due to a lung disease, because most often no lung lesions are detected on chest-films. In addition, the inspiratory dyspnea may not be attributed to tracheomalacia because the negative intrathoracic pressure during inspiration increases the diameter of the malacic intrathoracic trachea. Furthermore, compression of the thoracic trachea or an increased alveolar resistance causes retraction of soft parts of the thorax, but not the soft parts of the neck. Actually, the inspiratory retractions of soft part of the neck and suprasternal retractions should be considered a red flag sign of an obstruction of extrathoracic airways, which causes a strong negative pressure inside the cervical trachea.

One of the main characteristics of the respiratory problems due to a dysautonomic control of dilating upper airway muscles is that the inspiratory dyspnea, during the most severe phases, is associated with signs of expiratory

obstruction. The signs of expiratory dyspnea, which is usually transient, include expiratory ballooning of soft tissues of the neck, grunting, and contraction of abdominal wall muscles during expiration. Grunting may be easily distinguished from wheezing because with a stethoscope, it is possible to ascertain that the sound of grunting is loudest over the neck, whereas wheezing is loudest over the thorax. Most likely, the peak flow at the end of expiration (Fig. 10.1) is responsible for the expiratory ballooning of soft part of the neck, as well as of the "puffing" of cheeks [42].

The active expiration may become detrimental when the lung volume reaches a critical low volume. In this situation, any additional expiratory efforts, that is, crying, coughing, etc., may cause a sudden and massive collapse of widespread areas of the lung. The result will be a large right-to-left intrapulmonary shunt and hypoxemia that may cause ALTE. If the protective mechanisms to reverse ALTE are not efficient, a sudden asphyxial death may supervene [36]. Actually, about 3 % of infants with esophageal atresia or choanal atresia are found dead in their crib, and asphyxia seems the most reasonable cause of death.

About half of the infants with EA or with CA present feeding problems. In some infants with EA or CA feeding problems may be the only clinical manifestation. Sucking difficulties usually result in an unusually long feeding time. Pharyngeal dysphagia causes nasal regurgitation and/or laryngeal penetration. More than half of the patients present vomiting and/or gastroesophageal reflux. In infants with dysautonomia, feeding problems are considered the cause of a body weight in the lower centiles. However, clinical experience indicates that sometimes increasing the caloric support through a gastrostomy does not reverse failure to thrive, supporting the concept that in infants with dysautonomia, the metabolic cost of the increased work of breathing contributes to failure to thrive. Furthermore, many of these infants present a constitutionally low body weight [53]. The frequent association between respiratory and feeding problems may be explained with the consideration that the upper airway-dilating muscles are involved not only in the respiratory function but also in the functions of sucking and swallowing.

The concept that feeding and respiratory problems are mainly due to an anomalous autonomic regulation is supported by the frequent association with clinical manifestations of other autonomic dysfunctions. Bradycardia may be present even before birth during the last weeks of gestation and may be so severe to require an emergency caesarean section [37]. After birth, about 10–25 % of infants with CA or EA present episodes of bradycardia not associated with apneic spell and/or hypoxemia. Sometimes, bradycardia follows pharyngeal or tracheal suctioning; however, most often the mechanism triggering bradycardia is not identified. In one infant, during the course of esophageal repair, bradycardia was followed by cardiac arrest requiring cardiac message. This episode was probably the result of vagus nerve manipulation. Subsequently, this infant had two additional episodes of bradycardic arrest during esophageal dilatations under general anesthesia [37].

About one-third of the infants with EA or CA present profuse sweating during feeding or during sleeping. Sweating should be considered pathologic if the patient clothes became wet from dripping sweat. In one infant with EA, sweating associated with flushing was localized only on one side of the face and the body [37]. In infants with choanal atresia, this peculiar sign, that is unilateral sweating, was first reported by Richardson [1].

Additional dysautonomic features include sialorrhea, which should be considered significant if numerous daily replacements of wet bibs are required. Finally we considered as due to an anomalous regulation of body temperature the recurrent episodes of high body temperature without clinical or laboratory evidence of infection. These episodes of high temperature, previously observed in an infant with tracheal compression by an anomalous subclavian artery [16], usually last for few hours or days; however, they can be so severe to require parenteral rehydratation. One infant with CA

died during an episode of uncontrolled hyperthermia [35].

Associated Facial Anomalies

How to explain that infants with CA or EA present with a quite similar clinical features, enabling a common syndrome to be recognized?

As the autonomic nervous system develops from the neural crest cells, it has been postulated that these autonomic disturbances may be a manifestation of a neurocristopathy [13, 33]. This term was introduced by Bollande to describe a category of diseases arising from a maldevelopment of neural crest cells [9].

The number of neurocristopathies increased when Le Douarin and her colleagues with elegant animal experiments made fundamental acquisitions on the role of cephalic neural crest cells in the embryogenesis of cervicofacial region [11]. Accordingly, CA and the associated defects known as "CHARGE" association were considered the consequence of an abnormal contribution of cephalic neural crest cells to the development of nasofrontal bud [31]. As abnormalities in the migration of cephalic neural crest cells have profound effects on the embryogenesis of branchial arches [12], Pierre Robin syndrome [34] and DiGeorge syndrome were considered neurocristopathies of the first and second branchial arches, respectively [28].

To make sense out of the associations between CA, EA, and dysautonomia, we speculated that EA, CA, and dysautonomia may be related to an abnormal neural crest involvement. As facial anomalies are considered markers of a cephalic neurocristopathy [12], to test our hypothesis we studied the prevalence of facial anomalies in a series of infants with EA or CA, evaluated at a special follow-up clinic [39]. The association between CA and asymmetry of the face has been noticed since the first descriptions of clinical features of choanal atresia considered the result of "the same fetal condition that produces the choanal deformity" [1].

The facial anomalies were classified as follows: (1) anomalies of frontonasal process derivatives, (2) ear anomalies, and (3) asymmetric anomalies of branchial arches derivatives. Anomalies of frontonasal process derivatives included defects with a deficiency of ethmoid bone (flat nasal bridge, epicanthal folds, broad nasal bridge, and antiverted nares) or of other structures embryologically related to the frontonasal process (hypoplastic philtrum and/or upper lip, anomalies of maxillary incisors) (Fig. 10.2). Anomalies of the ears included one ear smaller than the ether, lop ears, deafness, structural anomalies of the pinna, low set ears, and preauricular tags or pits. Asymmetric anomalies of branchial arch derivatives included facial asymmetry (Fig. 10.3), unilateral facial paresis, and other unilateral facial dysmorphisms.

Overall, more than 90 % of infants with either CA or EA had one or more facial anomalies. About two-thirds of infants with choanal atresia and about one-third of infants with EA showed anomalies related to frontonasal process deriva-

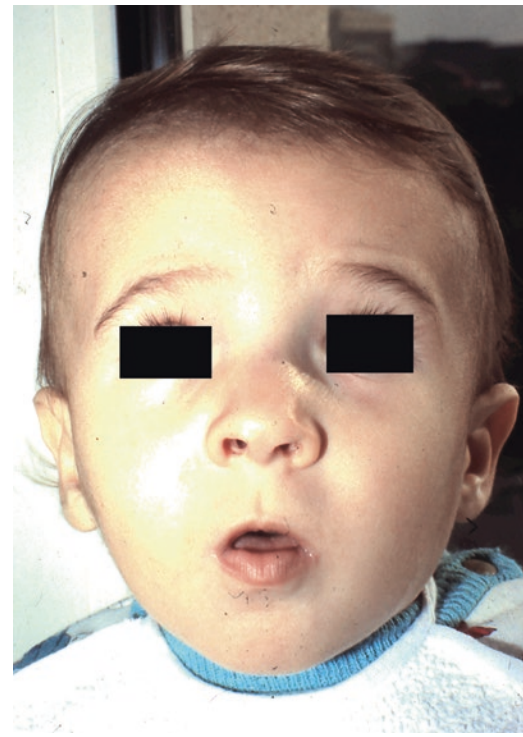

Fig. 10.2 Broad nasal bridge, hypoplastic nasal philtrum, hypoplastic upper lip, and antiverted nares in an infant with bilateral choanal atresia

tives. More than two-thirds of infants with EA and more than one-third of infants with CA showed asymmetrical facial defects. These two differences between EA and CA were statistically significant ($p=0.01$) [39].

Minor facial anomalies occur in about 40 % of normal infants with no major malformations and about 60 % of infants with major malformation [32]. Therefore, in infants with CA or EA, the overall prevalence of facial anomalies is significantly higher. In addition, the significant higher prevalence of facial anomalies related to branchial arch derivatives suggests that EA should be considered a branchial arch neurocristopathy. The striking pattern of neural crest-related cardiovascular anomalies (aortic arch anomalies, conotruncal defects, and superior vena cava malformation) associated with EA supports the concept that EA may be related to an abnormal contribution from the caudal portion of cephalic neural crest cells, which migrate into the fourth and sixth arches [45].

The main difference between facial anomalies associated is the higher prevalence of frontonasal process defects in infants with CA. This finding supports the concept that CA should be considered a frontonasal process neurocristopathy (ethmoidal syndrome) [31]. Finally, the association between of either CA or EA with a maturational dysautonomia may be explained with the contribution of cephalic neural crest not only to the cervicofacial structure but also to the autonomic nervous system [39].

The clinical implication of our observations is that the prevalence of facial dysmorphisms should alert the suspicion of a subclinical dysautonomia. Many facial anomalies are subtle and may pass unnoticed. However, minor facial anomalies should be evaluated and used as markers of other associated major anomalies as well as of an associated dysautonomia. As maturational dysautonomia may be involved in the pathogenic mechanism of SIDS, further studies should be designed to investigate if facial dysmorphisms may also serve to identify those infants at greater risk of SIDS [43].

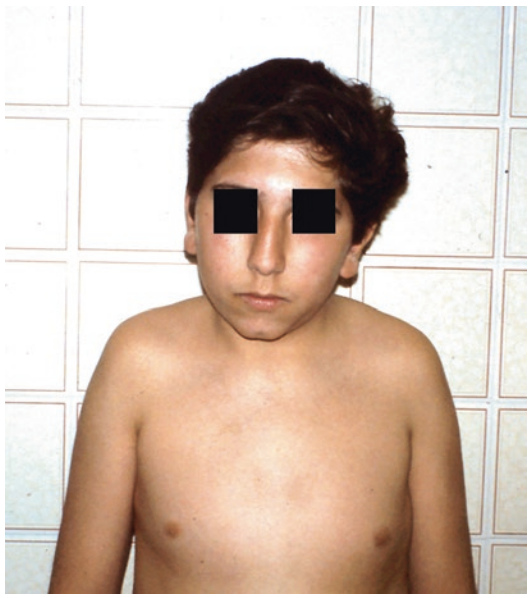

Fig. 10.3 Left side of the face smaller and flatter with the head tilted to the affected side in a patient with repaired esophageal atresia. An erroneous diagnosis of torticollis had previously been made

Relief of Vacuum-Glossoptosis-Apnea

In clinical practice various methods have been found valid for the prevention of asphyxial death related to recurrent episodes of partial or complete glossoptotic pharyngeal obstruction. In 1923, New reported that, in an infant with a "congenital flaccid tongue and palate" obstructing the pharynx, dyspnea and cyanosis during sleep were relieved by the insertion of a catheter into the pharynx through the mouth [2]. A similar observation was made by Hough in an infant with bilateral choanal atresia. In his view, the passage of a nasogastric tube through the mouth serves to break the seal on inspiration between palate and tongue [6]. Even in infants with "fatal respiratory distress" brought about by a rhinitis, a simple "mouth-tube" relieved the respiratory problems allowing respiration through and around the tube [8]. Similarly, relief of respiratory distress may be obtained by thumb-sucking in infants with micrognathia [4] or CA [20]. Another simple device, invented by the parents of an infant with bilateral choanal atresia, was a nipple with enlarged holes to assure efficient mouth breathing [7].

We observed that even a simple dummy may prevent cyanotic attacks in infants with bilateral choanal atresia (Fig. 10.4). Swift and Emery first observed that infants sucking dummies do not respond to induced nasal obstruction with signs of pharyngeal obstruction because they manage to keep the oral airway open [21]. Based on this observation, in 1979 we speculated that the use of a dummy may prevent some deaths in infants with sudden infant death syndrome (SIDS) [25]. Mitchell et al. tested our hypothesis with a case-control study and found that SIDS victims used a dummy during the last sleep very much less frequently than the infants of the control group [40]. Similar case-control studies were carried out in many countries around the world. A meta-analysis of these studies showed that the use of a dummy significantly reduces the risk of SIDS [49]. Based on these data, the American Academy of Pediatrics of North America recommends offering a dummy to infants at bedtime [48].

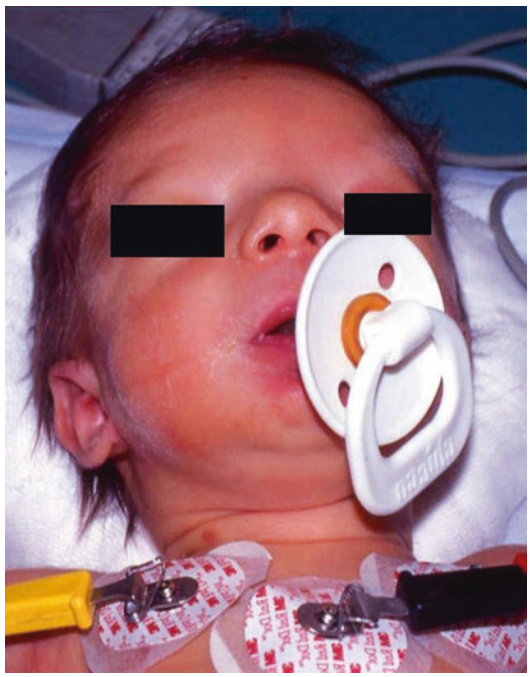

Fig. 10.4 Baby with bilateral choanal atresia is able to breathe through the mouth around a pacifier without respiratory distress

The role of glossoptosis-apnea in the pathogenic mechanism of SIDS was apparently disproved by the discovery that prone sleep position increases the risk of SIDS. In infants with Pierre Robin syndrome, prone position is traditionally considered a method to prevent glossoptosis-apnea because the force of gravity tends to bring the tongue forward. However, in infants with Pierre Robin syndrome, to avoid an obstruction of the upper airways in the prone position, the face is turned to one side, or the head is supported in a foam mattress in which a hole has been cut for the patient's face [34, 44]. An alternative method to avoid obstruction of the face and the nose in the prone position is a ventral suspension of the head by a stockinette cap.

International campaigns advocating a supine sleep position have resulted in a reduction of SIDS prevalence by more than 50 % [50]. The most accepted explanation is that prone sleeping position blocks the nose and the mouth and causes asphyxia, which seems to play an important role in many sudden deaths historically attributed to SIDS [51]. Therefore, sleeping in a prone position and the consequent potential upper airway obstruction are currently considered the most important extrinsic risk factors that may trigger SIDS [18].

In addition to the extrinsic factors, current evidence suggests that also intrinsic factors increase the risk for SIDS. Researches on the brain stem of SIDS victims suggest that the most important intrinsic risk factor is a dysfunction of the serotonergic system deputed to the modulation and integration of diverse autonomic functions [18, 52]. The regions of brain stem involved in SIDS victims are those deputed to the regulation of upper airway control, respiration, temperature, and other autonomic functions [18].

These data taken altogether strongly suggest that the old hypothesis that glossoptosis-apnea syndrome provides a model of sudden infant death that may be related to SIDS remains feasible [10, 25, 35, 47].

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Skeletal Anomalies Associated with Esophageal Atresia

11

Jonathan Nubla Sembrano, Walter H. Truong, Charles Gerald Tan Ledonio, and David Wayne Polly Jr.

Introduction

Associated anomalies, including those of the skeletal system, are commonly present in the setting of esophageal atresia (EA) or tracheoesophageal fistula (TEF). One of the more common scenarios for disruption of the esophagus and trachea is the VACTERL association. VACTERL is a mnemonic that stands for vertebral, anal, cardiac, tracheal, esophageal, renal, and limb anomalies.

The purpose of this chapter is to determine the incidence of musculoskeletal anomalies associated with esophageal atresia/tracheoesophageal atresia, the spectrum of skeletal anomaly involvement (upper limb, lower limb and spine), and the natural history, prognosis, and recommended treatment of these.

Search Strategy

A Pubmed search was performed in October 2009 as follows: First, various permutations and combinations of the term "esophageal atresia" and "tracheoesophageal atresia" were searched and combined (union). There were a total of 3,558 hits (A). Second, a search was conducted using the terms "musculoskeletal anomaly," "musculoskeletal deformity," "skeletal anomaly," "skeletal deformity," "vertebral anomaly," "vertebral deformity," "spinal anomaly," "spinal deformity," "limb anomaly," "limb deformity," and "congenital scoliosis." These searches were then combined (union); there were a total of 48,276 hits (B). Third, the intersection of A and B was obtained using the "AND" function. There were 295 hits (C). Fourth, a search was made on "VATER" and "VACTERL." There were 620 hits (D). Fifth, using the "OR" function, the union of C and D was obtained; there were 772 hits (E). These 772 titles were reviewed to ascertain relevance to the topic of skeletal anomalies; 80 titles were deemed appropriate for review (F). The abstracts of these 80 articles were then reviewed; 58 abstracts were deemed appropriate for review. The full-text articles of these 58 articles were then obtained and individually reviewed (WHT and JNS). Of these 58 articles, 53 were chosen for inclusion to this chapter.

There were 19 retrospective cohort studies of patients with esophageal atresia, tracheoesophageal fistula, or VATER/VACTERL association and looking at the incidence of skeletal anomalies (e.g., limb and spine). There were 25 case reports or small case series ($n<10$) describing rare or previously unreported skeletal anomalies

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associated with esophageal atresia. There were seven papers on the incidence of scoliosis or chest wall deformity as a consequence of thoracotomy for esophageal repair. There were two animal (rat) studies, one of which also had a clinical series described in the same paper. The other described a method for producing VACTERL-type malformations in rats by injecting Adriamycin during gestation [1]. Finally, one case control family study looked at the risk of associated anomalies in relatives of patients with esophageal atresia [2].

Occurrence of Skeletal Anomalies with Esophageal Atresia

Reported rates of musculoskeletal anomalies in patients with esophageal atresia range from 1.6 to 55 % [3–9] (Table 11.1).

The incidence of skeletal anomalies seems to rise when other atresias are also present. A 1976 paper by Gruchalski reported a 13.2 % incidence of skeletal involvement with esophageal atresia; this rose to 28.8 % and 40 % when there are anorectal atresia and anorectal + duodenal atresia, respectively [32].

In a retrospective comparative study, van Heurn et al. compared the incidence of skeletal involvement with EA between Asians and Europeans. They found no difference in rates (Asian 17 % vs. European 21 %) [8].

In a case control family study, Brown et al. found that associated skeletal malformations within the VACTERL association occur more frequently in relatives of individual with EA/TEF [2].

In an animal study by Abu-Hijleii et al., the researchers were able to produce skeletal anomalies in rat fetuses by injecting Adriamycin during the early gestational period. The authors theorized that vascular disruption of the mesoderm led to malformations and that the presence of the avascular mesenchymal interzone allowed for normal synovial joint development.

Limb Anomalies

The incidence of limb anomalies for the most part is not clearly delineated from that of general skeletal involvement in most published studies. In those that separated limb from spinal involvement, the incidence of limb anomalies in EA or VACTERL ranged from 8.9 to 42.7 % [9, 33, 34]. The most common form of limb anomaly is preaxial (radial) defect or deficiency, with an incidence of up to 35 % in VACTERL patients [33]. In a study utilizing pooled data from 11 birth defect registries, Rosano et al. found that the odds of having a preaxial defect is 4.3 times higher in those with esophageal atresia than those without [35].

Fernbach and Glass specifically looked at limb anomalies other than preaxial abnormality in 24 VATER patients. They described an expanded spectrum of limb anomalies, including Sprengel deformity, humerus hypoplasia, radioulnar synostosis, midline hand anomaly, clinodactyly, and syndactyly [36].

Lower extremity involvement includes tibial field defect, hip dysplasia, clubfoot, and other foot deformities [7, 11, 20, 21, 33, 34, 36, 37]. In a literature review by Castori et al., they found that among 24 VACTERL patients with lower extremity malformation, the most common type was that of tibial field defect (hypo-/aplasia) [11].

Spine Anomalies

Reported incidence of spinal anomalies in EA ranges from 6.9 % to 75 % [5, 9, 32, 34, 38–41]. These include vertebral hyper- or hyposegmentation, abnormal number of ribs, hemivertebra and wedge or butterfly vertebra, unsegmented bar, and congenital rib fusion (Fig. 11.1a–c).

Incidence of spinal anomalies in patients with the VATER/VACTERL association is much higher, with reported rates ranging from 66.4 to 100 % [33, 37, 42].

The occurrence of tethered spinal cord (TSC) appears to be higher when esophageal atresia is associated with an imperforate anus or any urogenital anomaly [43].

Mortality

Lower birth weight has been reported to be associated with higher incidence of associated anomalies, and the number of systems involved correlates directly with mortality. Isolated esophageal atresia had 0 % mortality; one other system involved had 3.2 % mortality, and two or more systems involved had 40 % mortality.

On the other hand, Keckler et al. in 2007 reviewed 112 EA cases and found that 63 % have associated VACTERL anomalies. They, however, concluded that although VACTERL anomalies are common, these have little impact on overall survival, which was 92.9 %.

Mortality also, however, is influenced by the time period of study, as technological advances in medical care allow for better survival. Okada et al. compared survival rates of EA patients among three time periods (1957–1967 vs. 1968–1980 vs. 1981–1995) and found improving survival: 27.8 % vs. 51.7 % and 80.4 %.

In a comparison of mortality rates between those with spinal involvement and those without, Bond-Taylor did not find significant difference

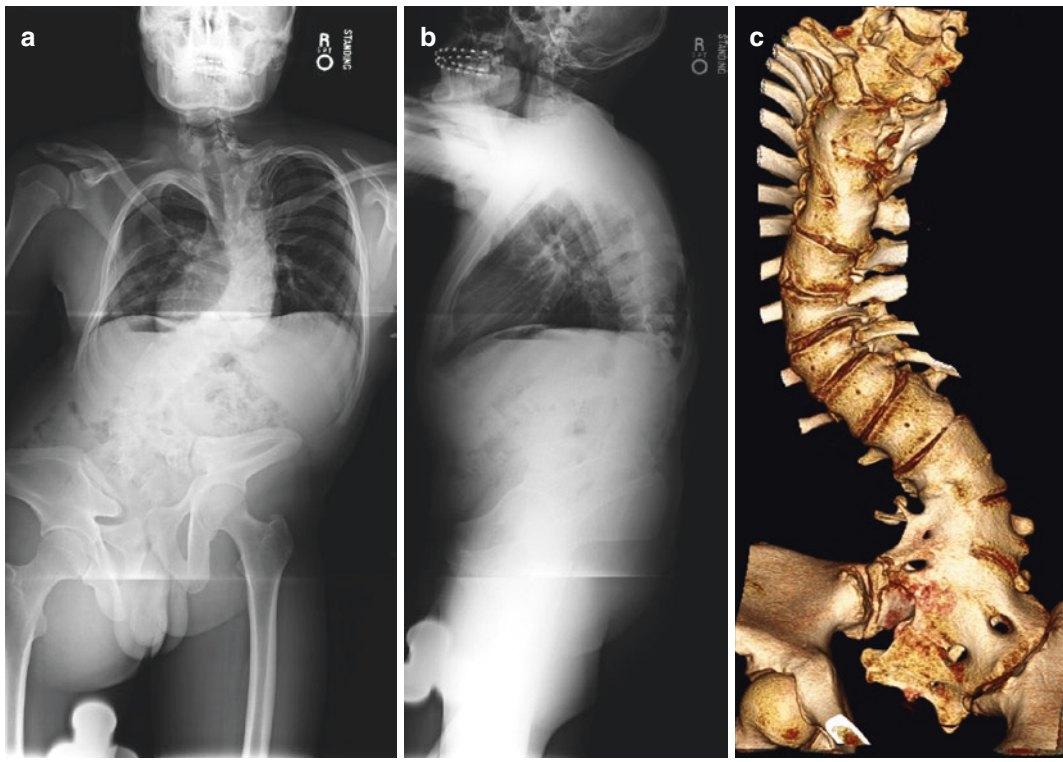

Fig. 11.1 (**a**) Anterior-posterior whole spine radiograph of a 17-year-old boy with VATER association showing severe congenital scoliosis with coronal plane imbalance. He also had a history of tethered cord release at 16 years of age. (**b**) Lateral view of the whole spine showing kyphosis with sagittal plane imbalance. (**c**) This is a three-dimensional reconstruction CT scan of the whole spine showing severe kyphoscoliosis and multiple vertebral anomalies which results in a coronal and sagittal plane imbalance.

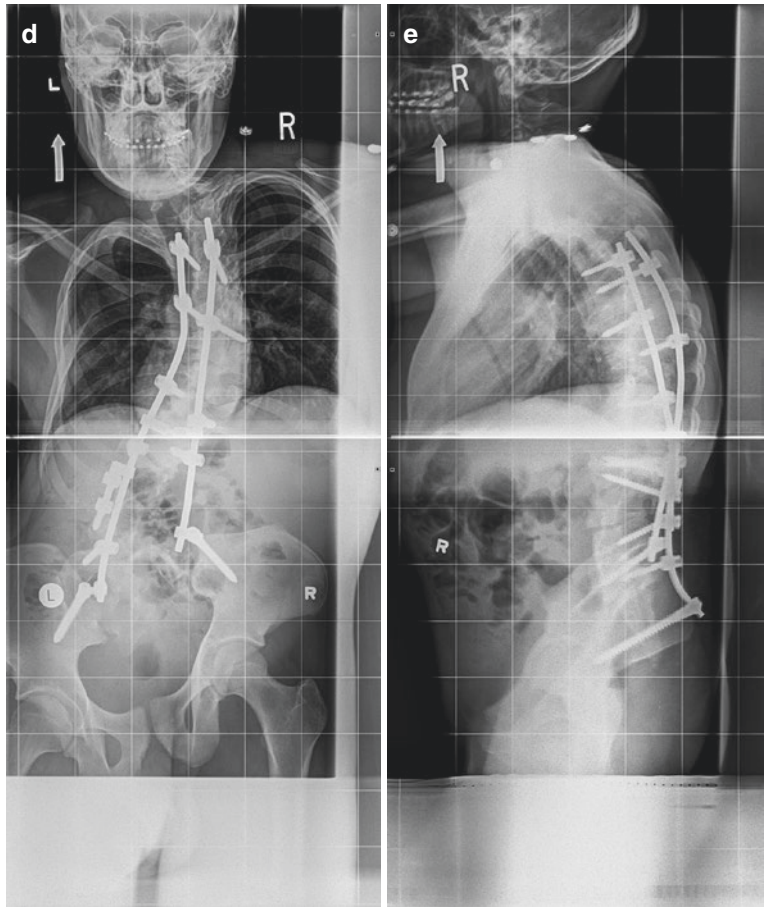

Fig. 11.1 (continued) (**d**) The patient underwent a two-stage instrumented spinal fusion to correct his severe kyphoscoliosis. This AP whole spine radiographs shows pedicle screw instrumentation from T2 to the pelvis. (**e**) This is the lateral view of instrumented spinal fusion

(with spine involvement 33 % vs. without spine involvement 24 %).

Atypical Presentations and Associations

Case reports of unusual presentations involving EA/TEF and skeletal malformation include reports of VACTERL with prune-belly syndrome [10], upper limb amelia [12], progressive torticollis [13], hydrocephalus (aka VACTERL-H) [17, 19], cleft hand [18], congenital absence of the long head of the biceps brachii [22], spondyloarthropathy-like presentation [23], bilateral tibial aplasia [24], partial hemihypoplasia [25], laryngeal stenosis [27], vertebral hypersegmentation [28], congenital absence of scaphoid [29], spinal dysraphism and tethered spinal cord [30], and CNS malformation requiring surgical intervention [31].

Other conditions or syndromes (non-VACTERL) that have also been reported to present with EA/TEF and skeletal anomalies include TAR (thrombocytopenia + absent radii) syndrome [14], Feingold (oculo-digito-esophago-duodenal or ODED) syndrome [15, 44], Gollop-Wolfgang complex (unilateral bifid femur with ectrodactyly) [16], sirenomelia [45], and tracheal agenesis [26].

Scoliosis Associated with Thoracotomy

The reported incidence of scoliosis after thoracotomy for esophageal atresia repair ranges from 19 % to 50 % [46–48]. Other sequelae described

include chest wall deformity, rib fusion with or without scoliosis, and breast disfigurement [44, 49] (Table 11.2).

Gilsanz et al. showed that the incidence of post-thoracotomy scoliosis is much higher among patients who develop dehiscence of their esophageal anastomosis than those who did not (57% vs. 0%) [51]. It was postulated by the authors that the mechanism of scoliosis development involved pleural scarring and rib fusion caused by disruption of the esophageal repair and subsequent leakage of contents.

Scoliosis after thoracotomy may either be concave or convex toward the side of approach. In the series of Westfelt and Nordwall, 75% (15/20) of cases were convex to the side of skin incision [48]. The authors hypothesize that pleural scarring on the side of approach causes concave scoliosis, whereas disruption of the costotransverse joints and intercostal and paraspinal muscles causes convex scoliosis.

Because of the high incidence of post-thoracotomy scoliosis, it is recommended that patients who undergo esophageal atresia repair through a thoracotomy approach be followed until skeletal maturity with regular scoliosis screening [50, 52]. In addition, Jaureguizar et al. concluded that alternative approaches to performing esophageal repair should be considered, in order to minimize the long-term sequelae associated with thoracotomy [44].

Treatment

Treatment of skeletal anomalies in the setting of EA/TEF requires a thorough assessment and good understanding of associated anomalies and overall prognosis. As a general rule, skeletal deformities are not as life-threatening as involvement of other organs; thus, treatment may be delayed until other conditions have been worked up and addressed. Once it has been established that the life expectancy and overall prognosis in regard to the nonskeletal anomalies are good, then the principles of treatment of the skeletal anomalies are the same as those in isolated cases (i.e., those not associated with EA/TEF) (Table 11.3).

Limb Anomalies

The goals in the treatment of limb anomalies mainly are preservation/optimization of function and cosmesis. For the upper extremity, motion, proprioception, and the ability to grasp are very important in achieving good function. For the lower extremities, equalization of leg lengths and correction of foot deformity to allow a plantigrade (foot flat on ground) stance are desirable goals, particularly in patients who are or are expected to be ambulatory.

Modalities used in treatment of limb deformities include surgery either in the form of amputation or reconstruction of the deformity; the use of casts, splints, prostheses, orthoses, and/or walking aids (crutches, walker, or wheelchair); physical and occupational therapies; and constant reevaluation.

Because limb deformities do change with growth, it is recommended that patients be followed until skeletal maturity.

Spine Anomalies

Scoliosis associated with EA/TEF may either be congenital or iatrogenic (post-thoracotomy). In either case, the focus of treatment in early-onset scoliosis (onset before 7 years old) is to allow growth of the chest cavity and maximize lung development.

Once a deformity is detected, patients should be evaluated regularly for progression of the deformity. In majority of cases, the scoliosis does not progress to the point of requiring fusion surgery. And in general, fusion is best delayed as reasonably possible, in order to allow as much growth of the spine as possible to occur.

Bracing may be instituted in an effort to halt curve progression. However, this requires careful consideration of patients' associated conditions, as a circumferential brace may be restrict breathing and limit access to the chest and/or abdomen.

Non-fusion surgical options that may find applicability in early-onset scoliosis include growth modulation via hemi-epiphysiodesis, vertebral stapling, and placement of conventional growing rods or a VEPTR (vertical expandable

prosthetic titanium rib) device. All of these are aimed at halting curve correction (with some curve correction) while still allowing spinal growth.

In patients with focal deformity (e.g., a single hemivertebra), short-segment fusion (with or without hemivertebrectomy) is preferable to a long-fusion construct.

Long-Term Results

Because of the very wide spectrum of presentation, as well as the relatively rare occurrence of the condition, there have been no high evidence level studies looking specifically at the effect of treatment of associated skeletal anomalies in patients with tracheoesophageal abnormality on long-term function.

It can be said, however, that long-term functional and cosmetic results of treatment of these skeletal anomalies are mainly dependent on the degree of the initial or underlying malformation, as well as the severity of associated abnormalities related to other organ systems. Patients who have minimal problems or limitations secondary to nonskeletal abnormalities may be expected to have the same functional results with treatment as those with similar but isolated skeletal anomalies.

Table 11.1 Case reports or small case series describing rare or new presentations of skeletal anomalies associated with esophageal atresia

Article	Country, years	N (male, female)	Spine anomalies	UE anomalies	Pelvis/LE anomalies	Misc
Ely et al. [10] Case report	USA (WV) 2008	1 (0, 1) VACTERL with pseudo-prune-belly syndrome	Scoliosis, decreased no. of ribs		Foot polydactyly	
Castori et al. [11] Case report	Italy	1 (1, 0) VACTERL with tibial developmental field defect	Hypoplastic ribs, hemi- and "butterfly" vertebrae	Clubhand (absent radius, thumb, and distal phalanx of the index finger); hypoplasia of the left scapula	Left tibia agenesis, clubfoot, hallucal deficiency, preaxial polydactyly	Lit review: 24 pts LE malformation: 68 % tibial hypoplasia/aplasia, 20 % fibular field defects
Pelluard-Nehme et al. [12] Case report	France	1 (1, 0) VACTERL with unilateral upper limb amelia	Butterfly vertebra, hemivertebrae, fused cervical vertebrae	Upper limb amelia, dysplastic scapula		Medically terminated at 22 wks gestation. Trisomy 18
Al Kaissi et al. [13] Case report	Austria	1 (0, 1) VATER with progressive congenital torticollis	9/f, with progressive torticollis treated with occiput-C1 fusion			Authors postulate that torticollis developed 2′ to congenital fusion between the atlas and occiput
Eren et al. [14] Case report	Turkey	1 (0, 1) TAR syndrome (thrombocytopenia + absent radii) with EA		Bilateral absent radii and thumbs		(+) family hx of consanguinity
Kellermayer et al. [15] Case report	Hungary	1 (1, 0) Feingold (oculo-digito-esophago-duodenal or ODED) syndrome with vertebral defects	Prominent sacral pit, anterosuperior ossification defects at L1, L2	Clinodactyly index and small fingers	Brachydactyly of toes, absent middle phalanges of all toes	
Erickson [16] Case report	USA (AZ)	1 (1, 0) variant of Gollop-Wolfgang complex (unilat bifid femur with ectrodactyly)			Bilateral clubfeet, right bifurcated femur, absent right tibia, absent left hallux	
Herman and Siegel (2004) Case report	USA (MO)	1 Feingold syndrome or MMT (microcephaly, mesobrachyphalangy, tracheoesophageal fistula)		Shortening of the index and small middle phalanges	Shortening of all middle phalanges	
Vatansever et al. [17] Case report	Turkey	1 (0, 1) VACTERL-H (VACTERL + hydrocephalus)	Fused L4–5	Right triphalangeal thumb		

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Table 11.1 (continued)

Endoh et al. [18] Case report	Japan	1 VACTERL with cleft hand	13 pairs of ribs, lumbosacral fusion abnormalities	Right cleft hand: preaxial syndactyly; absent middle and distal phalanges, short prox. phalanx of long finger		
Balci et al. [19] Case report	Turkey	1 (1, 0) VACTERL-H (VACTERL + hydrocephalus)	Multiple hemivertebrae	Bilateral triphalangeal thumbs		
Spoon [20] Case report	USA (MO)	1 (1, 0) VATER case study	Sacral fusion anomaly, 13 pairs of ribs	Bilateral shortened forearms, left radial clubhand, with 2 digits	Bilateral posterior hip subluxations	
Spruijt et al. [21] Case reports ($n=2$)	Belgium, Netherlands	2 (2, 0) VACTERL with tibial aplasia		#1 – Left radial ray defect and brachydactyly; right index-long cutaneous syndactyly, small finger clinodactyly	#1 – Absent left fibula, aplastic tibia #2 – Absent right tibia, cutaneous syndactyly of the left toes 2–3, 4–5	
Smith et al. [22] Case report	USA (HI)	1 (1, 0) VATER with absence of long head of biceps brachii	Tethered cord	Right rudimentary duplicate thumb, absent long head of biceps, hypoplastic superior labrum		
Erkan et al. [23] Case report	USA (NY)	1 (1, 0) VATER mimicking spondyloarthopathy	Fusion L1–L5, block vertebrae, butterfly T11			
Sozubir et al. 2000 Case report	Turkey	1 (0, 1) EA with sirenomelia	Caudal regression, vertebral anomalies		Sirenomelia (mermaid syndrome) – fused soft tissue of the lower extremities, normal bony hips, femurs, tib/fibs, feet	VATER may be a less severe form of sirenomelia, which is not compatible with life

Article	Country, years	N (male, female)	Spine anomalies	UE anomalies	Pelvis/LE anomalies	Misc
Basel and Goldblatt [24] Case report	South Africa	1 (1, 0) VACTERL with bilateral tibial aplasia	11 rib pairs, T6 hemivertebra	Right rudimentary (triphalangeal) thumb, absent 1st metacarpal, camptodactyly of the index finger, single palmar crease	Bilateral absent tibia, bilateral dislocated talus, absent great toes	
Chen et al. [25] Case report	Taiwan	1 (1, 0) VACTERL with partial hemihypoplasia	Right rib hypoplasia, scoliosis, multiple vertebral segmentation defects cervical and thoracic	Right hemihypoplasia: hypoplastic pectoralis, absent humerus and radius, short ulna, 3 metacarpals, 2 fingers		
Evans et al. [26] Case series ($n=5$)	Canada, Hungary	5 (3, 1, 1 NS) tracheal agenesis (TA); analysis of 100 cases pooled from literature	Vertebral anomalies 14 %	Radial ray defects 11 %	Lower limb deficiencies 3 %	Skeletal anomalies 38.1 %
Corsello et al. [27] Case series ($n=9$)	Italy	9 VATER/VACTERL	5 hemivertebrae; 1 additional congenital scoliosis	2 radial aplasias, 2 thumb hypo-/aplasias, 2 thumb duplication		Prefer VACTERL to VATER; "L" may refer to either the limb or larynx (1/9 had laryngeal stenosis)
Wulfsberg et al. [28] Case report	USA (MD) 1991	1 (1, 0) VATER with vertebral hypersegmentation	Hypersegmented vertebrae: 13 thoracic, 13 pairs of ribs, 7 lumbar		Bilateral hip dislocation, dorsiflexed feet	Propose that some malformations are 2′ to excessive flexion 2′ to vertebral hypersegmentation

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Table 11.1 (continued)

Treble [29] Case report	England	1 (0, 1) VATER with congenital absence of scaphoid	6 lumbar vertebrae, sacral agenesis	Absent scaphoid and radial styloid; hypoplastic 1st metacarpal and trapezium		
Chestnut et al. [30] Case series ($n=6$)	USA (CA) 1992	6 (1, 3, 2 NS) VATER with spinal dysraphism and tethered spinal cord (TSC)	#1: hemivertebra T9 to the sacrum; TSC 2′ to lipoma #2: vertebral defects; TSC 2′ to thickened filum with adipose tissue #3: vertebral defects; TSC 2′ to lipoma #4: hemivertebrae, TSC 2′ to lipoma #5: vertebral defects, TSC 2′ to lipoma #6: TSC 2′ to lipoma	#5: radial anomalies	#1: mild bilateral cavus feet #2: R foot deformity	Spinal dysraphism may have increased incidence in VATER Can diagnose TSC lipoma with ultrasound if less than 10–12 months of age
Raffel et al. [31] Case series ($n=4$)	USA (CA)	4 (3, 1) VATER with CNS malformation requiring neurosurgical intervention	#1: Severe kyphosis, segmental agenesis of the spinal cord at the level of T12 #2: L2–3 hemivert #3: T12-L1 hemivert, L3 spina bifida #4: severe cervical kyphosis with stenosis at 2 years old; quadriparesis at 3 years old after a fall	#3: bilateral radial agenesis, bilateral abducted thumbs	#1: R club foot #3: bilateral club feet	Suggest that all VATER patients be evaluated for neurosurgical malformations

Table 11.2 Articles describing development of scoliosis/chest wall defects after thoracotomy for repair of esophageal atresia

Article	Country, years	N (male, female)	Spine anomalies	UE anomalies	Pelvis/LE anomalies	Misc
Wong-Chung et al. [50] Case report	USA (NY)	1 (0, 1) scoliosis 2′ to rib fusion after thoracotomy for EA repair during infancy	9/F with scoliosis (47°, concave toward thoracotomy); 6th–10th rib fusion; treated with rib fusion mass resection			Patients who had thoracotomy for EA repair should be followed up to skeletal maturity for scoliosis screening
Westfelt and Nordwall [48] Retrospective cohort	Sweden 1972–1978, f/u in 1988	61 (33, 28) EA patients who underwent lateral thoracotomy for EA repair in childhood Looked at the development of scoliosis Mean age at thoracotomy 7 years, mean age at f/u 20 years	20/61 (33 %) developed scoliosis (24 % in boys, 43 % in girls) 15/20 convex to the side of incision Only two >20 deg curve; none underwent surgery for scoliosis			Hypotheses Pleural scarring causes curve concave to incision Disruption of costotransverse joints and muscles cause curve convex to incision
Chetcuti et al. [46] Retrospective cohort	Australia 1948–1985, f/u 1986–1987.	302/538 EA/TEF patients were interviewed/examined for long-term follow-up for the development of spinal deformity	58/302 (19 %) developed spinal deformity 51/302 (17 %) had congenital vertebral anomaly, but only 47 % developed clinical deformity 34/251 (14 %) without anomaly developed scoliosis			Scoliosis associated with mixed vertebral anomalies in lower thoracic spine had worst prognosis in terms of curve progression. Recommend careful follow-up of patients with vertebral anomalies

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Table 11.2 (continued)

Chetcuti et al. [46] Retrospective cohort	Australia	285 EA/TEF patients who had thoracotomy for repair and with long-term follow-up for the development of chest wall deformity (CWD)	99/285 (35%) developed CWD 22/53 (41%) of those with congenital vertebral anomaly developed CWD 77/232 (33%) of those w/o congenital vertebral anomaly developed CWD, and 20/232 (13%) developed scoliosis 2/3 of scoliosis were concave toward the side of incision			Anterior chest wall deformity more common in patients > 25 years old Breast surgery to minimize inequality was required in three patients
Gilsanz et al. [51] Retrospective cohort	USA (CA) 1966–1980	82 thoracotomy for EA, w/o vertebral malformation Looked at the development of scoliosis, follow-up 2–17 years	8/14 who had dehiscence of esophageal anastomosis developed scoliosis ≥20°, concave toward incision 0/54 w/o dehiscence developed scoliosis			Scoliosis after EA repair seen only in those with disruption of surgical anastomosis, leading to subsequent pleural scarring and rib fusion
Durning et al. [47] Retrospective cohort	USA (OH) 1960–1970	18 (8, 10) thoracotomy for EA/TEF Looked at the development of scoliosis, follow-up ≥10 years	9/18 developed scoliosis 8/9 concave toward incision 5/9 >20°. 2/9 >40°, 1 underwent spinal fusion			Curves that develop before puberty are more likely to progress. Early childhood thoracotomy needs careful observation for scoliosis development
Jaureguizar et al. [44] Retrospective cohort	Spain 1965–1981	89 thoracotomy for TEF with long-term follow-up (3–16 years) Looked at the sequela of thoracotomy	18 (20%) thoracic wall asymmetry 9 (10%) rib fusion 7 (7.8%) severe thoracic scoliosis 3 (3.3%) breast disfigurement	21 (23.8%) "winged" scapula 2 (2.2%) shoulder LOM 2′ to cicatrix		Dorsolateral thoracotomy may lead to significant musculoskeletal complications, should consider alternative approach
Dunlay et al. [52] Case report	USA (IA)	1 (0, 1) scoliosis 2′ to rib fusion s/p thoracotomy for TEF	22/f, 50° left convex T1–T8 curve. Fused right ribs 3–4, 4–5			Treated with PSF T2–L1. Recommend scoliosis screening post-thoracotomy

Table 11.3 Retrospective cohort studies of patients with EA/TEF/VATER/VACTERL looking at the incidence of skeletal/limb/spinal anomalies

Article	Country, years	N (male, female)	Spine anomalies	UE anomalies	Pelvis/LE anomalies	Misc
Eghbalian et al. [3] Retrospective cohort	Iran, 2002–2008	63 (25, 38) EA. Looked at associated anomalies		1 absent radius		1/63 (1/6 %) skeletal involvement
De Jong et al. [42] Retrospective cohort	Netherlands 1988–2006	90 (58, 32) with ≥2 VACTERL defects, normal karyotype Looked at non-VACTERL-type anomalies	62 (68.9 %) vertebrae/ribs: 50 vertebrae, 37 ribs	29 (32.2 %): 16 radial, 18 thumbs, 6 preaxial polydactyly		70 % had non-VACTERL anomalies, e.g., single umbilical artery (20 %), genital defects (23 %)
Kuo et al. [43] Prospective observational	Taiwan 2001–2004	9 (4, 5) VACTERL w/ imperforate anus Looked at tethered spinal cord (TSC)	7/9 had TSC; 6/7 of those with urogenital anomalies had TSC			Recommend MRI for all VACTERL w/ imperforate anus or urogenital anomaly
Keckler et al. [34] Retrospective cohort	USA (MO) 1985–2005	112 (62, 50) esophageal atresia Looked at VACTERL anomalies	24.1 % vertebral anomalies (4.4 % tethered cord, 3.5 % butterfly vertebra, 4.4 % fused vertebra, 4.4 % hemivertebra, 1.8 % additional vertebra, 5.3 % additional or absent ribs)	8.9 % upper limb anomalies (3.5 % absent radius, 6.2 % digital anomaly) If (+) vertebral anomaly, 28.6 % chance of limb abnormality	0.8 % hip dysplasia	Only 37 % have isolated TEF VACTERL anomalies common but have little impact on overall survival (92.9 %)
van Heurn et al. (2001) Retrospective comparative study	China, Netherlands 1982–1998	European 34 (20, 14); Asian 48 (25, 23) EA Looked at associated anomalies	Asian – 1 vertebral European – 6 vertebral	Asian vs European: polydactyly 2 vs 2; syndactyly 2 vs 1; other 3 vs 2		Musculoskeltal involvement similar, Asian 17 % vs European 21 %

(continued)

Table 11.3 (continued)

Rosano et al. [35] Pooled data from 11 birth defect registries	Europe (Italy, Finland, France, Israel, Netherlands, Spain), USA, Mexico, Argentina (ICB-DMS = International Clearinghouse for Birth Defects Monitoring Systems) 1983–1993	1983–1993 666 (366, 300) non-syndromal limb defects with at least one other major anomaly Out of 5,163,958 live and stillborns		Preaxial defects with EA 53 cases; odds ratio 4.3; Prevalence of preaxial defects 5.4/100,000		Preaxial limb defects occurred more frequently with distinct malformations, including esophageal atresia
Rejjal [4] Retrospective cohort	Saudi Arabia 1980–1995	89 (54, 35) EA/TEF. Looked at associated anomalies	4 vertebral, 1 hypoplastic ribs, 1 with 13 pairs of ribs	2 absent thumbs, 1 absent radius, 1 clubhand, 1 bilateral absent radii		7 (8 %) with musculoskeletal anomaly
Xia et al. [9] Retrospective cohort and animal study	Spain 1965–1997	443 EA. Looked at associated skeletal anomalies Rats: Adriamycin at GD 8–9 ($n=16$) and control ($n=4$).	Patients: 37.5 % hypersegmentation; 4.9 % hyposegmentation; 31.8 % extra ribs; 17.5 % missing ribs; 19.1 % vertebral body anomalies Rats: 100 % vertebral defects if with EA	Patients: Preaxial 25.6 % Rats: 4/31 with EA had limb osseous malformations		245/443 (55 %) of EA have skeletal anomalies Adriamycin-treated rat fetuses as VACTERL animal model Theory: Hox family gene dysfunction

Article	Country, years	N (male, female)	Spine anomalies	UE anomalies	Pelvis/LE anomalies	Misc
Saing et al. [7] Retrospective comparative study	Hong Kong 1982–1993	41 (19, 22) EA <2 systems involved ($n=31$); ≥2 systems involved ($n=10$)	1 scoliosis, 2 sacral dimple	2 poldactyly, 1 syndactyly	1 bilateral equinovarus	17 % incidence of skeletal anomalies. Lower birth weight associated with higher incidence of assoc. anomalies No assoc. anomaly: 0 % mortality <2 systems involved: 3.2 % mortality ≥2 systems involved: 40 % mortality Overall mortality: 12 %
Okada et al. [40] Retrospective comparative study	Japan 1968–1995	159 EA ± TEF I (1957–67): $n=18$ II (1968–80): $n=29$ III (1981–95): $n=112$	14/159 (6.9 %) vertebral anomalies	5 (3.1 %) radial defect 3 (0.6 %) polydactyly		Survival rate improved by period I = 27.8 % II = 51.7 % III = 80.4 %
Botto et al. [33]	USA, Italy, Brazil, Norway, Mexico, New Zealand, Hungary, France, Australia, Spain, Israel, Japan	286/10 million infants had VATER association	66.4 % axial skeleton defects	3.5 % transverse limb deficiencies	14 % deformations (clubfoot, hip dysplasia)	VAR 74 (25.9 %)
Pooled data from 17 birth defect registries	(ICB-DMS = International Clearinghouse for Birth Defects Monitoring Systems) 1983–1991	51/286 had at least four VATER anomalies 8/286 with all five anomalies	0.3 % sirenomelia	35 % preaxial limb anomalies (deficiencies and polydactyly) 3.8 % other limb deficiencies (postaxial and intercalary deficiencies, split hand/split foot)		A.T.E.R. 55 (19.2 %). 74.8 % with VATER had other non-VATER defects

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Table 11.3 (continued)

Rokitansky et al. [5] Retrospective cohort	Austria 1960–1991	309 EA Looked at associated malformations	9.1 % vertebral anomaly 3.9 % rib anomaly 1.0 % Klippel-Feil syndrome	1.9 % radial aplasia 1.0 % thumb malformation 0.6 % clavicle malformation	1.0 % foot malformation	162/309 (17.8 %) skeletal malformations
Rokitansky et al. [6] Retrospective cohort	Austria 1975–1991	223 EA Looked at associated malformations				17.9 % skeletal malformations
Fernbach and Glass [36] Retrospective cohort	USA (IL) 1979–1986	24 (17, 7) VATER with no chromosomal abnormality Looked at limb anomalies other than radial defect or preaxial abnormality		2 Sprengel deformities 3 humerus hypoplasia 1 radioulnar synostosis 1 midline hand anomaly Other: clinodactyly, syndactyly, shortened phalanx, rotary malposition of digit	3 LE long bone absence 1 ft nonaxial hypoplasia 2 ft syndactyly	Authors describe expanded spectrum of limb anomalies in VATER association
Lawhon et al. [4] Retrospective cohort	USA (OH, DE) 1969–1982	28 (16, 12) VATER Looked at orthopedic anomalies	100 % had Vertebral anomaly 16 congenital scoliosis (hemi-/butterfly/wedge vertebrae, unsegmented bar, rib fusion) 5 sacral agenesis 7 combined sacral dysgenesis and vertebral anomaly	13/28 radial dysplasia (absent/hypoplastic/bifid thumb, absent radius) Other: radial clubhand, hypoplastic humerus, congenital elbow fusion	3 hip dislocation 1 proximal femoral focal deficiency 2 absent tibia 1 congenital vertical talus	7/28 had limb deformity other than radial dysplasia 12/28 had undergone 17 ortho procedures

Article	Country, years	N (male, female)	Spine anomalies	UE anomalies	Pelvis/LE anomalies	Misc
Gruchalski et al. [4] Retrospective cohort	England	791 esophageal (EA)/duodenal (DA)/anorectal atresia (AA) Looked at the incidence of skeletal anomalies	20/280 (7.1 %) of EA have spine anomaly 1/9 (11 %) of EA + DA have spine anomaly 7/45 (15.6 %) of EA + AA have spine anomaly 2/5 (40 %) of EA + DA + AA have spine anomaly	17/280 of EA have digit/radius anomaly 2/9 of EA + DA have digit/radius anomaly 10/45 of EA + AA have digit/radius anomaly 1/5 of EA + DA + AA has digit/radius anomaly 2 phocomelias	2/280 EA have major LE abnormality 1/9 EA + DA has major LE abn 1/45 EA + AA has major LE abnormality	40 % skeletal anomaly in triple atresia (EA + DA + AA) 13.2 % in EA 11.1 % in EA + DA 28.8 % in EA + AA
Stevenson [41] Retrospective cohort	USA (MD) 1952–1971	44 EA/TEF Looked at spinal anomalies	33/44 (75 %) extra vertebrae			
Janssen and Kemperdick [39] Retrospective cohort	Germany	20 EA Looked at spinal anomalies	10/20 (50 %) abnormal number of vertebrae (1 hyposegmentation) 7 (35 %) vertebral malformation 5 (25 %) 13 rib pairs			
Bond-Taylor et al. [38] Retrospective cohort	England	40 EA/TEF Looked at spinal anomalies	15/50 (37.5 %) 9/40 (22.5 %) 13 rib pairs 6 (15 %) 6 lumbar vertebrae 3 hemivertebrae 1 LS spina bifida	1 bilateral absent radii	1 talipes equinovarus	11/40 (27.5 %) mortality rate: 5/15 (33 %) in vertebral anomaly group, 6/25 (24 %) in normal spine group (NSD)

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Part IV

Repair of Shorter Gap EA

History of the Treatment of Esophageal Atresia

12

John E. Foker

Introduction

The story of esophageal atresia (EA) is as fascinating and varied as the lesions themselves. EA comprises a wide spectrum of defects, ranging from an absent or atretic segment commonly referred to as pure EA through lesions which have one or more associated tracheoesophageal fistulae (TEF) [1]. The first understanding of EA comes early but only much later and after many different surgical attempts to correct these lesions is anything like reasonable success achieved. Most early efforts dealt with the common form of a blind upper esophageal pouch and lower tracheoesophageal fistula (about 80–85 % of the total) but the other types also contribute to the story [2]. The history can only be recounted from what has been published; nevertheless, the thinking about and struggling with these babies and even the poignancy of repeated failures come through clearly.

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Pre-repair History

The first accurate portrayal of both the clinical and anatomic features of an infant with esophageal atresia and tracheoesophageal fistula was by Thomas Gibson in 1697 [1]. The infant's greedy attempts at feeding, followed by convulsive choking and later by death, were subsequently explained by the postmortem findings of a blind upper pouch with a distal tracheoesophageal fistula.

Probably because of the futility of attempting to treat the lesion, the story seems to unfold slowly. When traced through the literature, over a century passed without the birth defect again being mentioned. Even well into the 1800s, only a few cases are added to the world's apparent experience. Hirschsprung (1861) described four cases collected over a 7-month period from his then small city of Copenhagen and added these to ten others that had been reported [3]. The scattered reports and presumably by word of mouth led Mackenzie (1880) to suspect that these lesions were not extremely rare [4]. Presumably the lesions were occurring at an incidence of approximately 1 in 2,500–3,500 births, but the result was always the same – death [5–7].

The few case reports in the nineteenth century which both described the clinical and pathological picture indicated there was an appreciation of the lesions themselves. These cases must also have stimulated thinking about a possible repair

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and although success would come much later, it was recognized early that a primary repair of esophageal atresia would be the preferable treatment. In the *Surgical Management of Children's Diseases*, Holmes (1869) suggested that the esophageal ends could be joined together when a fistula was not present [8]. A gastrostomy was the first surgical treatment recorded, however, and was based on the obvious need for hydration and nutrition. It was recognized that a gastrostomy would not solve the entire problem and, in a baby with EA/TEF, could make matters worse. SP Steele (1888) was apparently the first to place a gastrostomy in one of these infants with the hope that only a rupturable membrane existed between the esophageal segments. Unfortunately, that was not the case [9].

The early reports recognizing the defect and the long, heartfelt discussions on the attempts at treatment have been more extensively recounted by Ashcroft and Holder and, especially, Myers [6, 10]. The reader is directed to these articles to provide a more complete picture of this fascinating journey. It seems certain, however, that the discussions of possible modes of therapy and the recognition of the determinants of success and failure by individuals must have far exceeded those appearing in the literature.

The surgeon who might have moved the treatment of EA/TEF substantially ahead was Richter, who recognized in 1913 both the desirability and impracticality then of a primary repair [11]. He also knew that gastrostomy alone would fail and so used positive pressure anesthesia, probably for the first time in an infant, to ligate the fistula intrathoracically. Unfortunately, the patient did not live long enough to address the problem of the blind upper pouch. Richter accurately described the problems one encounters when trying to surgically control the fistula and might have succeeded had he operated on additional infants. His approach would prove useful decades later as the staged repair in unusually premature or sick infants [12].

Both gastrostomy placement and fistula ligation were considered necessary after Richter's report, but Smith noted that gastrostomy alone was still being tried repeatedly without success [11, 13]. Vogt, for example, described six cases, five of which were treated and were unsuccessful [14]. Even jejunostomy would not solve the problem because gastric secretions stimulated by feeding could still enter the trachea. Because the ligation of the TEF could not be carried out with hope of success, it proved an insurmountable problem for nearly two more decades.

Even as the era of survival approached, recognition of EA was one thing and effective treatment was quite another. Gage and Ochsner (1936) reported being unsuccessful in treating six infants over 15 months [15]. At that time, the consequences of the EA/TEF spectrum were so damaging to the infant that a reliably successful repair would depend more on the development of better methods of caring for the critically ill infant and less on new surgical techniques.

The early accounts of the surgical attempts to treat the EA spectrum graphically revealed what would be the necessary components of success. Effective treatment would require control of the upper pouch to prevent aspiration and ligation, or division, of the fistula to eliminate reflux into the trachea. Both of these consequences had predictably led to fatal pneumonias in the pre-antibiotic era. Control of the TEF, however, made it necessary to be able to adequately ventilate the infant when the chest was open. If aspiration and reflux could be controlled, gastrostomies were available and quickly became important for hydration and nutrition to allow survival of more than a day or two. Much had to be in place before the technical details of a primary esophageal repair came into play.

The initial survivors were isolated and relatively unusual cases of the spectrum which did little to advance the treatment of infants with EA or affect the struggle for reliable treatment. Their survival was almost fortuitous as they made it through the potential early problems so that repair could come much later. The first survivor was born in 1931 with a TEF and no EA, but did not undergo repair until 1935 [16]. Repair was done through a transtracheal incision, and a residual fistula was closed a short time later. The first survivor of pure esophageal atresia was born in 1936 and maintained with gastrostomy

feedings until reconstruction was carried out much later by a jejunal interposition [17]. These two anomalies were at the opposite ends of the spectrum. More importantly, they were single problems with a favorable situation, and the repair could be begun later without a thoracotomy incision.

The far more common combination of a blind upper pouch and a lower TEF located in the midthorax proved much more difficult to treat. The accounts of Lanman and Haight were particularly poignant [18, 19]. Deaths following these operations were commonly due to pneumonia or mediastinitis, and effective antibiotics were unavailable. Even fluid management was poorly understood, and the infant who might have become the first survivor of a primary repair apparently died from overhydration produced by excessive continuous intravenous fluids. Lethal dehydration, however, was equally likely to occur in the preoperative period [20].

Although the early surgical attempts to treat EA with a TEF showed an understanding of the necessary components of a reliable repair, the methods tried varied widely and generally failed to solve the problems. The 32-patient series recounted by Lanman described the varied surgical approaches taken by a number of famous surgeons to solve the problems of EA/TEF [18]. Either right or left posterior incisions were made with wide extrapleural approaches to avoid entering the pleura because of the uncertainties of positive pressure ventilation. After dividing the musculature, four to six ribs were sectioned and the center two removed to provide generous access. Attempts to deal with the proximal and distal esophageal ends were hindered by poor airway control or the problems imposed by the need for positive pressure ventilation if the pleural space was entered. Several surgeons divided the fistula and brought the distal end out the back, which controlled the reflux and provided a site for feedings, but the ends tended to slough and retract, and mediastinitis raged [18].

Because an abdominal incision might be better tolerated, the fistula was ligated near the stomach and a gastrostomy placed, but spillover of the lower esophageal secretions into the trachea still occurred. This concept was carried further by dividing the stomach with the proximal end brought out to drain the lower esophagus and a gastrostomy placed in the distal half. Spillage into the trachea, however, still occurred and the ventilatory capacity suffered with large fistulae [21]. Division of the lower esophageal segment, with the upper end oversewn and the distal end brought out to serve as a feeding gastrostomy, fared no better [22].

All attempts at treatment of esophageal atresia prior to the late 1930s were unsuccessful. Preoperative preparation was ineffective, and the infants usually went to surgery in critical condition. Rehydration, treatment of existing pneumonias, and control of the upper pouch were not satisfactory. The condition prior to surgery could not readily be reversed, and the operation did not halt the deterioration.

Even when the first survivals occurred, whether following staged procedure or a primary repair, the reasons for success were not apparent, and the case descriptions were similar to previous discussions of failure. Success came twice, 1 day apart, in 1939. Leven at the University of Minnesota and Ladd at the Children's Hospital of Boston placed gastrostomies in two infants with esophageal atresia and tracheoesophageal fistula [23, 24]. Despite the presence of a fistula, small feedings in these two instances did not prove fatal, and the fistulae were not ligated until 5 weeks and 4 months later, respectively. Cervical esophagostomies were performed much later, and more years elapsed before Leven provided continuity with a jejunal interposition and Ladd completed construction of an antethoracic skin tube [24, 25]. Although the firsts, both patients had survived having a TEF for many weeks and did not resemble the usual circumstances.

The First Primary Repairs

The first successful primary repair, by Haight in 1941, broke another long spell of failures [26]. A primary repair had been attempted but without survival at least 11 times by several surgeons beginning as far back as 1923, including twice by

Haight himself and twice by Alexander at their institution [27, 28]. This was clearly a milestone but the reason for success this time was not apparent. The successful anastomosis was begun under local anesthesia, but the esophageal ends could not be brought together without quieting the infant by open drop ether anesthesia. The primary repair was accomplished, but survival in this case occurred despite such overhydration as to produce sclerema. In addition, there was an anastomotic leak with presumed mediastinitis, and the patient was not discharged from the hospital until she was 20 months of age. Nevertheless, this breakthrough broke the spell; success began to come more frequently, and by 1944, a third of these infants survived primary repair [29].

Over the next two decades, the advances which occurred rapidly on all fronts – preoperative preparation, antibiotic therapy, and intraoperative and postoperative management – allowed primary repair in favorable circumstances to become reliably successful. As has often been the story when new surgical fields have been opened, the operative capabilities were present before overall care was sufficient to help the patient withstand the stresses of the operation. During the late 1940s, the reliability of primary repair improved, and in one series, remarkable for the time, short-term survival was 80% [30]. Nevertheless, results in the 1940s and 1950s varied widely as centers struggled to improve care and surgeons wrestled with operative details [31]. Not all EA/TEF patients were in the same condition for an operation, and the classification of Waterston proved valuable in where to direct efforts [32].

Further Refinements and Continuing Issues

The emergence of antibiotic therapy was perhaps the single most important reason for the new success, but almost as significant were the rapid advances in anesthesiology, postoperative management, and the emergence of newborn intensive care units. During this period, there was also a great deal of surgical innovation. Anastomotic leaks were a serious problem from the first cases on, and a variety of techniques were tried to avoid them. Although the first successful primary repair was made with a single-layer anastomosis, the common problem of leaks led to two-layer repairs. After the inner row of muscular sutures was placed, the muscular wall of the upper pouch was pulled down over the first layer and anchored lower down on the esophagus to cover the anastomotic line [17, 19]. These two-layer techniques provided more security against leak, but the trade-off was a greater tendency to stricture formation from the turn-in of the tissue. As is well recognized, the problem of anastomotic leak has only been reduced in incidence and not entirely eliminated. Anastomotic strictures and gastroesophageal reflux also remain problems. Because strictures and GER remain significant, they are taken up in much more detail in separate chapters within this book.

The commonness of postoperative strictures and the persisting dysmotility of the lower segment found after primary repair led to the development of an end-to-side anastomotic technique [5, 33, 34]. The rationale was that limiting the dissection of the lower esophagus to just beyond the fistula might better preserve the blood supply and the vagus nerve and, with them, esophageal function. A large opening could be made in the lower esophagus which did reduce stricture formation, but leaks remained a problem. Unfortunately, recurrent fistulization occurred too frequently even if the mucosa was stripped from the fistula before tying. Dilation of a stricture after this repair ran the additional risk of reopening the fistula. Dysmotility, moreover, was similar to other repairs because the contraction wave passes through the muscular layer and is interrupted with any anastomosis. With exceptions, this operative approach is not generally used [35].

Primary repair is made most difficult by a long gap between esophageal segments, and even today this remains an important surgical problem. Early on, it was recognized that the consequence of a gap between the ends meant anastomotic tension. Several strategies were proposed to reduce the tension that would jeopardize

a primary anastomosis. Suture techniques to lessen tension varied from placement of elaborate mattress sutures that overlapped the anastomosis to the use of traction sutures anchored in the paravertebral tissue [24, 29, 36]. Other methods, such as upward traction on a catheter anchored at the stomach entrance, were tried in order to reduce tension [37]. These and related techniques have never become popular because of the problems they produced or the limited applicability. The problem of long-gap atresia was reliably first solved by interposition grafts; however, as will be discussed in other chapters, they bring their own consequences. More recently, a variety of techniques including the use of circular myotomy have been used and increased the incidence of primary repair when the gap is not overly long [38]. Despite these many efforts, the problem of long-gap EA remains today and is the subject of other chapters in this book under: The Repair of Long-Gap EA; The Growth Procedure for Long-Gap EA, and Interposition Procedures to Establish Continuity.

All these operative variations reflected the increasing emphasis placed on technique as surgeons attempted to solve the variety of problems encountered in the esophageal atresia spectrum. The discouragement of failure after failure was left behind, and the emphasis shifted to refining the techniques and care so that smaller and sicker infants could be included in this success. Primary repair of esophageal atresia became the epitome of pediatric surgery, which it remains to this day. It is frequently the pediatric surgeon's favorite operation and programs are often judged by the yearly number of EA/TEF cases [6, 39].

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Preoperative Evaluation

13

H. Till

The detection of a polyhydramnion during a prenatal ultrasound investigation raises the suspicion of an EA/TEF. Also a paucity of fluid in the upper oesophageal portion or the failure to detect a gastric bubble could point towards an impaired gastrointestinal passage in the fetus [1]. However, neither of these parameters nor their combination has a significant predictive value [2]. On the other hand, these findings are of major clinical importance, because those children should be delivered in centres with considerable experience in treating children with EA/TEF.

Most infants with EA/TEF become symptomatic soon after birth with excessive salivation (drooling), choking or coughing. In newborns with type C EA, the gastrointestinal tract may be continuously insufflated via the lower TEF. Thus abdominal distension and impaired diaphragmatic movements contribute to an increasing respiratory insufficiency. Such neonates should be kept "nothing per os" (NPO) and investigated immediately by passing a 12-French nasogastric tube gently into the oesophagus. If there is any resistance and if it fails to reach the stomach, an EA must be ruled out. The 12-French tube could be exchanged for a Replogle suction tube, and further studies are initiated to confirm and classify the malformation.

A regular X-ray film of the chest including the neck and upper quadrants of the abdomen usually reveals most of the important features of any EA, which are (a) the type of atresia, (b) the gap between the oesophageal remnants and (c) the presence of anatomical or genetic malformations.

The presence versus absence of gas below the diaphragm determines the classification: If the abdomen is filled with gas, a lower TEF (type C) must be present (Fig. 13.1), and vice versa if the abdomen is gasless, a pure EA (type A) must be anticipated (Fig. 13.2). Assuming that a pure EA is most likely associated with a considerable gap between the oesophageal remnants, most paediatric surgeons would refrain from a primary repair immediately after birth and place a gastrostomy instead, for early enteral feeding and later evaluation of the lower pouch (see below).

In children with type C, the distance between the upper pouch and the TEF is assessed primarily, because the surgical management depends on the length of the gap. That is what this textbook is all about!

Before taking a chest X-ray, a nasogastric tube is advanced maximally into the upper pouch and thus marks its deepest point (Fig. 13.1). A contrast medium may be used only in unclear situations and with extreme care, because the pouch easily fills with just a few millilitres, and laryngeal

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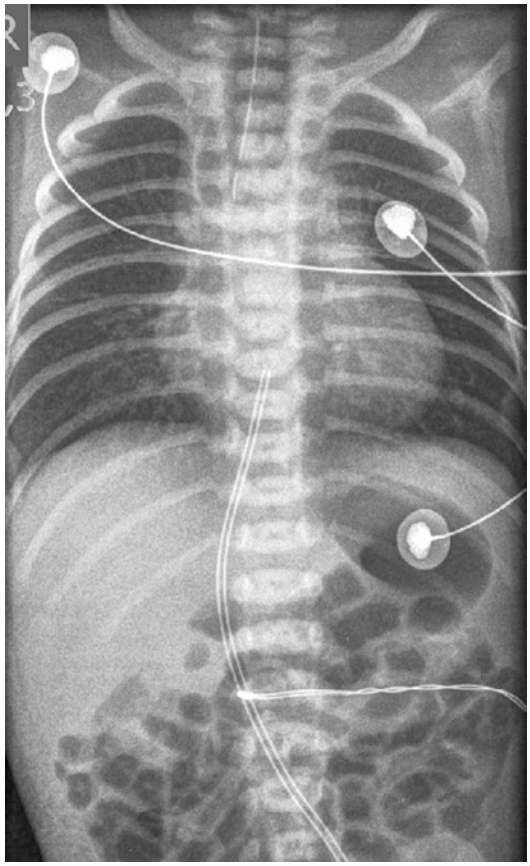

Fig. 13.1 X-ray of a newborn baby with an EA/TEF (type C). The tip of the Replogle tube marks the lowest point of the upper pouch. The TEF allows for gas passing into the gastrointestinal tract

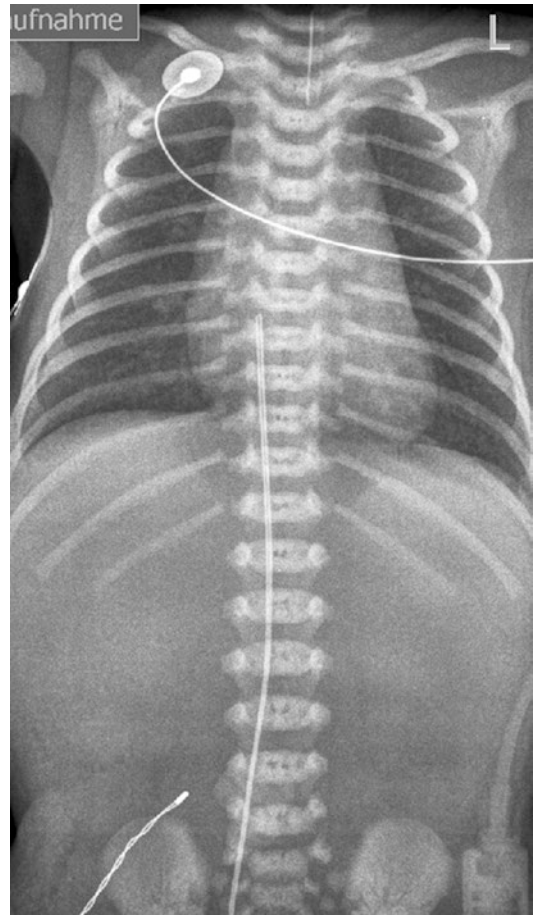

Fig. 13.2 X-ray of a newborn baby with a pure EA (type A). The tip of the Replogle tube marks the lowest point of the upper pouch at approximately the level of the clavicles. No gas is passing into the gastrointestinal tract

overspill could cause aspiration and pneumonia. However, when an upper TEF must be ruled out, this investigation is useful. Recently, K. Bax investigated his children with pure EA and found an incidence of a proximal fistula of more than 50 % [3]. Alternatively, such anatomical questions can also be answered during a preoperative tracheobronchoscopy. Even rare forms of trachea-bronchial malformations, such as laryngotracheal clefts, must be kept in mind.

Concerning the lower oesophageal remnant, a plain chest X-ray is only sufficient in the presence of a TEF. Usually, the TEF originates from the membranous portion of the trachea close to the bifurcation. Thus the gap between both oesophageal remnants can be estimated by measuring the distance between the lowest point of the upper pouch and the bifurcation of the trachea [4]. Per definition, we consider a distance of more than 3 cm or three vertebral bodies as long-gap oesophageal atresia (LGEA).

In cases of pure EA, the distal oesophageal remnant can be easily assessed once the gastrostomy has healed. Retrograde filling of the stomach with contrast medium and simultaneous fluoroscopy outline the endoluminal anatomy (Fig. 13.3). However, this investigation may be false negative, if there is no adequate influx into the distal pouch, e.g. due to a competent lower oesophageal sphincter. Consequently, a direct investigation by fibre-optic endoscopy and simultaneous fluoroscopy (Fig. 13.4) may be

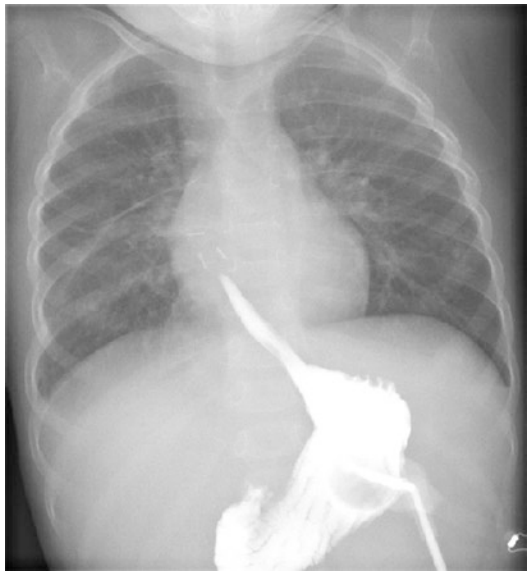

Fig. 13.3 Radiographic investigation of the lower oesophageal remnant in a 1-year-old child with LGEA. He had treated by traction sutures (the metal clips are marking the extraluminal end of the pouch. Contrast medium has been installed via the gastrostomy into the stomach and is delineating the length and the lumen of the lower pouch

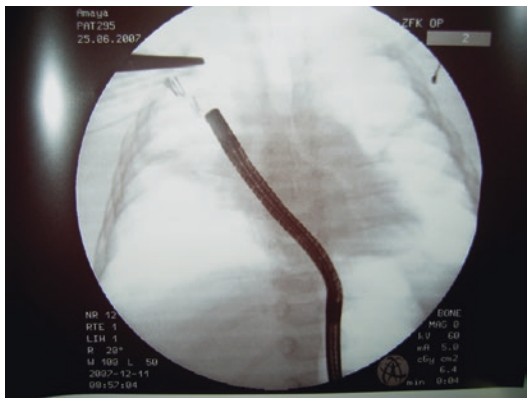

Fig. 13.4 Direct investigation of the lower pouch (during "Foker elongation" with clips on both pouches) by fibre-optic endoscopy and simultaneous fluoroscopy

more accurate [5]. In very small infants, when even the smallest endoscope does not fit through the gastrostomy, a 10-French nasogastric tube with a radiopaque guide wire could be used instead.

Besides the type of EA and the length of the gap, every child with EA must be investigated for associated malformations. As mentioned in Chap. 8, an EA can occur as an isolated form (without further malformations), as an associated form (e.g. with VACTERL malformations) or as a syndromic type (e.g. trisomies 13 or 18 or 21). Besides a careful clinical investigation for visible anomalies, a cardiologic assessment including an echocardiography is essential. Cardiac and aortic anomalies like a right-sided descending aortic or a double aortic arch may be identified preoperatively [6]. However, it should be noted that the sensitivity of the echocardiography in detecting abnormalities of the aortic arch is limited and that intraoperative "surprises" must be encountered anyhow [7]. We will deal with the adequate strategies and surgical manoeuvres in Chap. 14. An ultrasound investigation of the abdomen and kidneys (see Chaps. 8, 9, and 10) supplies additional information.

Finally, in cardiorespiratory stable neonates with an EA/TEF, the repair is usually performed within the first 24 h of life. In the meantime the Replogle tube is kept under continuous suction. An endotracheal intubation should be avoided until the child is positioned on the operating table, because the tube may not seal the TEF adequately and any ventilation would thus inflate the stomach. Gastric perforation is a well-recognised complication of EA/TEF and is usually associated with extreme prematurity and requirement for assisted ventilation [8]. Thus babies with a respiratory insufficiency and gross gastric distension must be considered as an emergency. Before finally positioning the child on the operating table on its left side, it is advisable to perform a tracheobronchoscopy [9] to define the origin of the lower TEF in relation to the bifurcation and to exclude an upper TEF. Furthermore, it facilitates positioning the tip of the tube just distal of the TEF and enables intraoperative reassessment of its location in the vent of a cardiorespiratory instability [10]. This completes the preoperative evaluation.

Acknowledgement We thank Dr. Ina Sorge, Department of Paediatric Radiology, University of Leipzig, Germany, for supporting this article with the X-rays depicted below.

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Thoracotomy Incisions

14

John E. Foker and Adrian Bianchi

Introduction

Almost as many different thoracotomy incisions have been described as the number of esophageal repairs that have been proposed. For much of the history of esophageal atresia (EA) repair, the only question in making these incisions was how to obtain the best exposure without considering the functional or cosmetic consequences. While exposure is of major importance, more recently, much more consideration has been given to the incisions themselves as the longer-term consequences have become more apparent [1–6]. The purpose of this chapter, therefore, is to present the principles behind incisions that will provide very adequate exposure while minimizing the late consequences. With these principles in mind, we will present in more detail the incisional approaches which fulfill these criteria best.

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The Standard Incision

The incision itself should be placed along the skin lines in order to minimize scarring and keloid formation. If the skin orientation cannot be determined by inspection, or by gently pinching the skin, Langer's lines are diagrammed in most anatomy textbooks. In general, these lines circle the patient's trunk; therefore, transverse incisions are preferable.

The site of the incision itself should be governed by two factors: the location of the organ to be repaired and the structures overlying the chest wall which will be damaged by the incision. In addition, the old justification that "wounds heal from side to side not end to end" does not acknowledge the fact that the longer the incision, the more likely that important structures will be injured and that other longer-term problems will emerge with time.

The patient is positioned in a straight lateral position with the arm bent over the head. The down leg is bent to reduce the rolling tendency. The patient is taped as shown. The tape along the undersurface of the upper arm adds stability and tends to increase the opening. The tape across the hip ensures stability (Fig. 14.1). In general, weighted (sand) bags provide little help in

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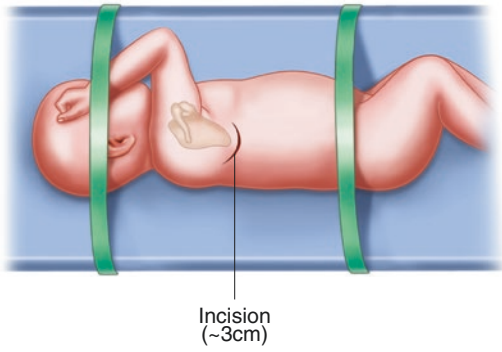

Fig. 14.1 In a straight lateral or slightly tipped forward position, with the lower leg bent to reduce rolling, tapes are applied as shown. The patient will remain fixed and stable. By applying one piece of tape along the undersurface of the upper arm and anchoring it superiorly, it will tend to "open" the chest wall. Padding should be placed between the legs. Sandbags are cumbersome and do not provide stability of the right chest wall which is the point of entry for reaching the esophagus. A 3 cm posterior lateral incision will be ample for EA repair in newborns. For older children, a 4 cm or slightly longer incision should be adequate. To reduce the consequences of the thoracotomy incision, the serratus anterior muscle should be spared in its entirety, and, posteriorly, the incision should not divide any peri-spinal ligaments and muscles. To gain access to a high upper pouch, it will be useful go through the fourth or even third interspace instead of the commonly used fifth (fourth) interspace. In this case, a second intercostal opening will usually be required to reach the lower esophageal segment

stabilizing infants and may impede access by pushing posterior and anterior chest tissue upwards and collapsing the opening. Sandbags, nevertheless, are almost an article of faith in some operating rooms.

The standard thoracotomy incision for EA repair begins with a transverse skin incision about 1 cm posterior and about 1.5 cm inferior to the tip of the scapula and carried posteriorly until the paraspinal muscle group beneath it is reached (Fig. 14.1). In a 3–3.5-kg newborn, this incision need only be 3 cm in length to provide adequate access for the surgeon. For the assistant, and others at the operating room table, however, the view will be very limited. Once the chest is opened, a thoracoscopic telescope can be placed through another rib interspace which will provide good visualization for all in the room.

At the next layer, the serratus anterior muscle is not incised at all, and the long thoracic nerve and vascular bundle carefully preserved as will be the mechanics of the shoulder girdle. The latissimus dorsi muscle is opened a bit longer than the skin incision. Posteriorly, the paraspinal ligaments should be preserved completely to limit the likelihood of scoliosis.

The interspace opening should be longer than the skin incision to allow an adequate opening. The interspace is easily opened by inserting and pushing with the tip of a slightly opened Metzenbaum scissors (a push cut). The scissors are inserted into the intercostal muscle about 2 mm above the upper margin of the lower rib. The vascular bundle within the lower margin of the upper rib is not damaged, and the lower rib is not denuded, which lessens rib fusion and the development of scoliosis. The intercostal incision itself should be made closer to the upper edge of the lower rib to avoid the neurovascular bundle in the rib above. A chest retractor is inserted and gradually opened at intervals to increase the opening. After a little time and successive increases in the spread of the retractor, a large opening can be made without breaking the ribs.

For the standard EA with lower tracheoesophageal fistula (TEF), the interspace at or just above the incision provides very adequate access to the upper and lower esophageal segments and the fistula itself. The choice of the intercostal opening, however, can easily be varied using this same skin incision. If the upper pouch is unusually high, the intercostal incision should be at least one interspace higher. An important point to remember is that if one finds the intercostal incision either too low or too high, another intercostal opening can be made through the same skin incision. For a very small lower esophageal segment that does not reach the diaphragmatic hiatus, a second intercostal (not skin) incision two interspaces lower will provide better access to it. Making the intercostal opening lower than the sixth interspace will not be helpful and, moreover, may place part of the incision into the diaphragm.

With pure esophageal atresia and a long gap, therefore, the standard skin incision would be made, but two intercostal incisions will be used; one through the third and another through the sixth interspace. The two intercostal incisions will provide direct access to the upper and lower

esophageal segments through a single skin incision. The skin incision in infants and children, moreover, is quite flexible. This flexibility together with the ability to change the intercostal entrance into the pleural space means that the skin incision does not have to be long and the important thoracic muscles and ligaments can be spared.

The Axillary Incision

An axillary incision has been used and perfected by one of the authors (AB). The cosmetic advantages are obvious, as are the preservation of thoracic muscles and shoulder mechanics. Consequently, there is much to recommend this incisional approach advocated by a superior surgeon. For those able to gradually gain familiarity with this unconventional approach, it should be used. The only disadvantage that will likely cause difficulty, in the opinion of the other author (JEF), is carrying out the location and mobilization of a very small (diminutive) lower esophageal segment.

The lung will be retracted medially and superiorly revealing the parietal pleura overlying the esophagus.

The Intrathoracic Component

The question of whether to use an extrapleural or intrapleural approach has been long debated although most surgeons choose an extrapleural approach for the repair of a straightforward EA/TEF. The extrapleural approach allows the mobilized pleura to drape over and seal the anastomosis; however, it has not convincingly diminished the incidents of leaks or other problems. When a leak or disruption occurs, this approach provides no advantage and may make repair of the problem more difficult. The combination of a leak and subsequent stricture which requires an esophageal resection is made much more difficult with an adherent pleura. The planes become difficult to identify, and important structures such as the aorta may be included in the resulting scarring.

For a growth procedure, with traction sutures on the esophageal segments, an intrapleural approach is necessary. The smooth intrapleural surfaces allow the esophageal segments to move easily with growth. If the segments are retropleural, however, the pleura drapes over them and becomes adherent, quickly halting progress.

Another point of discussion is whether or not to ligate and divide the azygos vein as it turns toward the superior vena cava where it will be in close proximity to the esophageal repair. If a second operation is needed and the azygos vein is left behind, it may be adherent to the back of the esophagus, where it can be injured. If the azygos vein is very large, however, it may be the result of an inferior vena cava interruption, and the vein must be preserved and the anatomy understood.

Over the years, a number of other incisions have been used by surgeons in order to gain adequate exposure for the dissection and repair of the EA spectrum. These have ranged from a long vertical posterior incision requiring the division of a number of ribs to a long transverse incision in which the serratus anterior and other chest wall muscles are divided. When compared to the incisions discussed above, they have many detrimental consequences and should not be used.

Thoracoscopic (Minimally Invasive) Approach

More recently, spurred on by the realization that long incisions would likely produce significant chest wall deformities as the child grew, as well as their virtual absence when minimally invasive surgical (MIS) procedures are used, thoracoscopic repairs have been more frequently used. With this experience, the MIS results have also improved.

Conclusions

At the present time, a trade-off exists between the short incisions for an open repair and the lesser incisional consequences of an MIS thoracoscopic approach. Currently, the thoracoscopic approach with its attendant larger needles and sutures which can be only placed and tied one at a time and the loss of dexterity ("touch") by the use of long instruments makes this approach a reasonable choice only for the straightforward type C (blind upper

pouch and tracheal fistula to the lower pouch) lesions with a short gap between the two segments. With a longer gap, the inability to use multiple back row sutures to gradually bring the ends together and tie each suture off tension makes MIS a less satisfactory choice. After all, it is the avoidance of a serious complication such as partial disruption of the anastomosis and the quality of the repair itself that will be very important to the infant's quality of life from that time forward.

Although it must be acknowledged that as the gap length increases and, with it, the anastomotic tension, the likelihood of a significant postoperative stricture and the presence of GE reflux also increases. These problems, however, are quite treatable, and, if corrected in infancy, these children can enjoy the ability to eat normally and have outwardly normal esophageal function. The goal, again, is 70+ good years.

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The Current Repair Techniques of Short-Gap EA/TEF

15

H. Till and M. Hoellwarth

Introduction

With the advances in neonatal minimal invasive surgery (MIS) and successes in elaborate reconstructive procedures, such as the repair of esophageal atresia [1], a neonate with an EA/TEF in contemporary times has the option to be approached either by thoracotomy or by thoracoscopy [2]. Irrespective of the access route preferred, the basic operative steps remain identical between the two approaches and comprise the closure of the TEF and a primary anastomosis of the esophageal ends. Since the minimal invasive technique will be described in detail in the following chapter, this article focuses on the open, "traditional" access only.

Surgical Techniques

Most pediatric surgeons approach a short-gap EA/TEF from the right side [3]. Even EA/TEF cases with a right-sided aortic arch have been suggested for this approach by several authors [4–6]. Concerning a detailed preoperative workup, we refer to Chap. 12. If a preoperative bronchoscopy is planned, which we recommend to exclude an upper pouch fistula and to determine the position of the TEF, it should be performed before positioning the child for a posterolateral thoracotomy. Thereafter, the child is placed on his/her left side, and the chest is raised with a soft towel to widen the intercostal spaces. The right arm should be placed anteriorly over a padded face and flexed in the elbow to prevent injury to the brachial plexus (Fig. 15.1).

Most surgeons prefer a horizontal or slightly curved skin incision located just at the tip of the scapula. A vertical incision in the midaxillary line or a high axillary skin crease incision has also been advocated [7]. In order to minimize surgical trauma, the intercostal spaces are approached by a muscle sparing and atraumatic dissection of the latissimus dorsi muscle and the serratus anterior muscle [8]. When entering the fourth (or fifth) intercostal space, the operation progresses with an extrapleural mobilization. The main objective for this strategy is to minimize the risk of an empyema in case of an anastomotic leak. With the general acceptance of a thoracoscopic approach, this dogma has been challenged. The present literature reveals no obvious benefits, when the two approaches, trans- or retropleural, are compared [9]. For such an extrapleural preparation, the parietal pleura is bluntly peeled off the thoracic wall down toward the dorsal mediastinum using a wet swab. The azygos vein represents a major landmark in any

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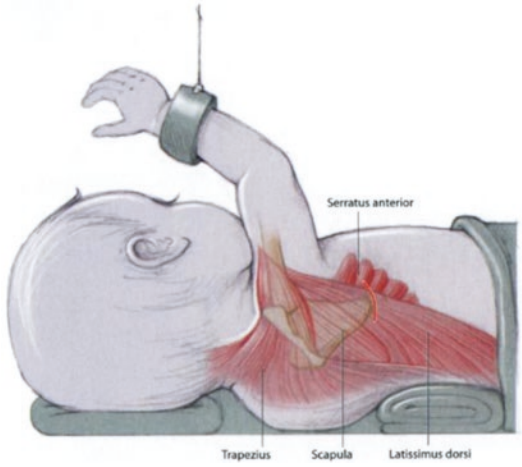

Fig. 15.1 (Drawing from Prof. Höllwarth): Positioning of a child with EA/TEF for a right-sided posterolateral thoracotomy

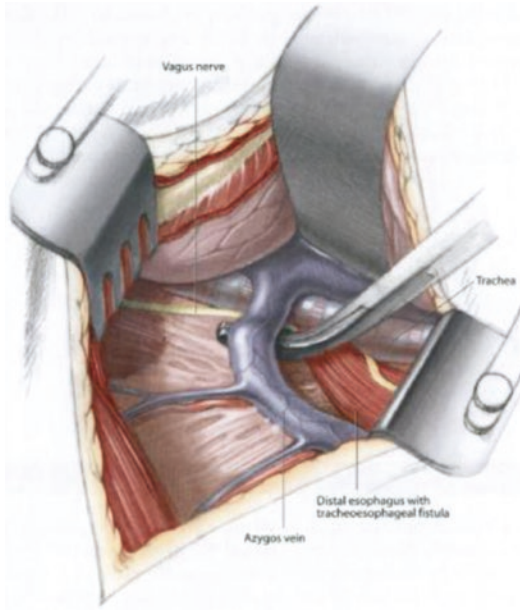

Fig. 15.2 (Drawing from Prof. Höllwarth): The azygos vein represents a major landmark of any EA/TEF operation. Its dissection is not necessary, but usually quite helpful to identify the TEF

TEF repair (Fig. 15.2). Dissection of the vein may not be necessary, but it certainly facilitates an easier identification of the TEF. Next, the vagal nerve fibers should be identified as they converge to the distal esophagus. The distal esophagus is encircled with a vessel loop to permit an atraumatic mobilization (Fig. 15.3). Usually, it is more hypoplastic than the upper pouch, and extensive dissection is not recommended in order to preserve the blood supply and vagal innervation. Instead the TEF is mobilized straightforward to its junction with the trachea. Especially, in preterm babies, this preparation should be performed with great care to avoid damaging the membranous portion of the trachea. The TEF should be divided close to the tracheal wall, leaving a small cuff of approximately 1 mm (Fig. 15.4). This cuff is closed with interrupted 5-0 sutures. It seems worth mentioning that some experts postpone this maneuver until they have assessed the length of the upper pouch and have made a decision about the feasibility of a primary repair.

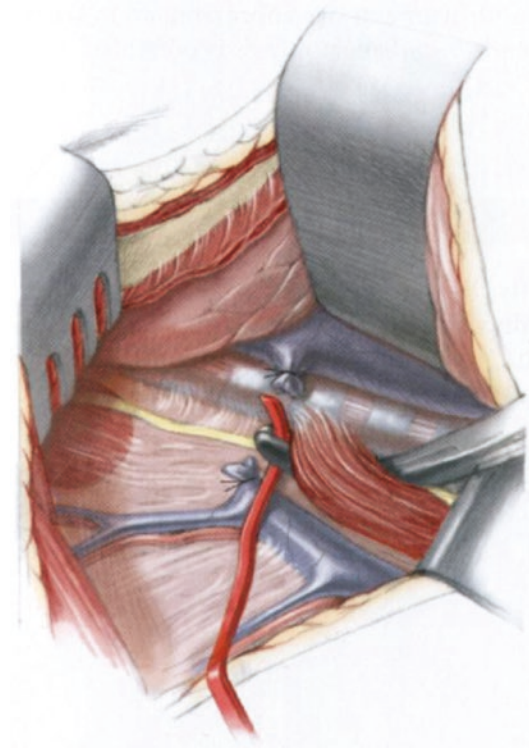

Fig. 15.3 The TEF has been encircled with a vessel loop to allow for an atraumatic preparation. Vagal nerve fibers have been preserved

In order to facilitate identification of the lowest portion of the upper pouch, a Replogle suction tube or a larger nasogastric tube placed in

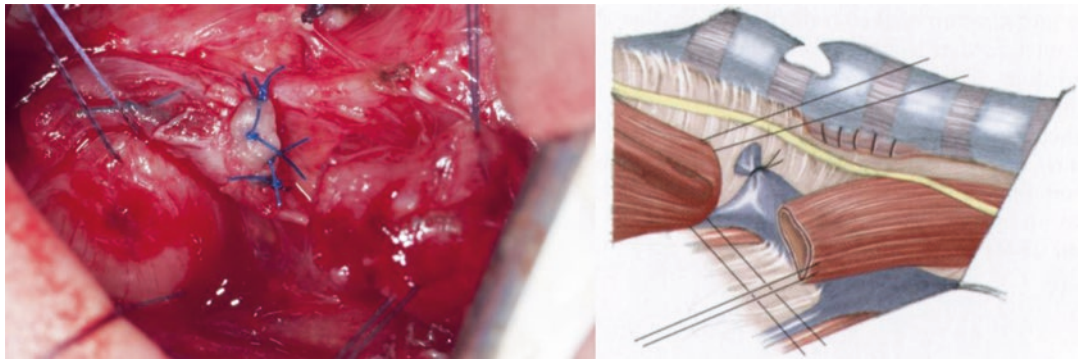

Fig. 15.4 Short-gap EA/TEF in a neonate weighing 2,000 g with duodenal atresia. The TEF has already been dissected and closed with interrupted 5-0 Prolene sutures. Two 5-0 Vicryl sutures are marking the upper pouch (still closed) and lower TEF (same anatomical situation as a diagram on the left)

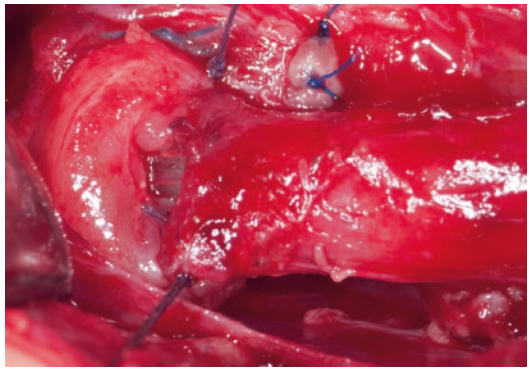

Fig. 15.5 Same case as in Fig. 15.4. The posterior part of the anastomosis has already been fashioned. A transanastomotic drain (8-French feeding tube) has been passed down into the stomach

the upper pouch is gently pushed by the anesthesiologist. Traction sutures are placed on either side of the tip. Since the upper pouch often shares a common wall with the membranous portion of the trachea, special care is essential during the mobilization. We prefer a sharp dissection as it minimizes a collateral damage to the trachea or recurrent laryngeal nerve. Once the pouch has been mobilized completely and the decision for a primary repair has been made by approximation of both segments, the tip is incised. Pushing the Replogle tube may help to define the lowest point. It seems important to mention that the opening of the mucosa must be sufficient large to avoid stenosis later.

Several techniques of an end-to-end anastomosis in EA/TEF have been reported [10, 11]. Techniques worth debating would be single versus double layer, interrupted versus continuous suturing, absorbable versus nonabsorbable material, and of course inverted versus everted knotting. However, there is no evidence in the present literature that any of these parameters offer advantages to their counterpart. In most cases, a single-layer reconstruction with interrupted sutures seems straightforward. We prefer to place the corner stitches in an outside-in and inside-out fashion, always taking "a good bite" of the muscular wall including the mucosa (Fig. 15.5). However, the remaining stitches of the posterior wall do not necessarily have to be on the outside, if tying would stress or twist the anastomosis. If some tension is anticipated, it may be advisable to place all posterior sutures first without tying them right away. Instead, the sutures are then crossed one by one to gradually advance the esophageal ends. This maneuver can be repeated until the esophageal remnants have approximated and the sutures can be tied. Once the posterior suture line has been finished, we pass an 8-French feeding tube into the stomach for stenting of the anastomosis (Fig. 15.5), for postoperative gastric decompression, and for enteral feeding on the first postoperative day. However, the placement of a transanastomotic tube is not supported by a large body of evidence in the literature [12]. Finally, the anterior aspect of the anastomosis is

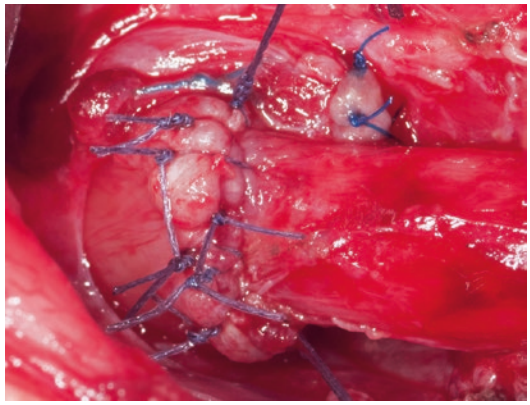

Fig. 15.6 Final aspect of the anastomosis with interrupted sutures and extraluminal knots

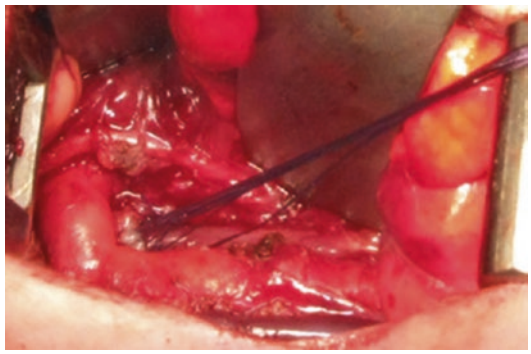

Fig. 15.7 A child with an EA/TEF and a right-descending aorta. For the primary esophageal repair the child has been approached from the right. Thus the aortic arch crosses the upper pouch and the anastomosis lies just distal and underneath it

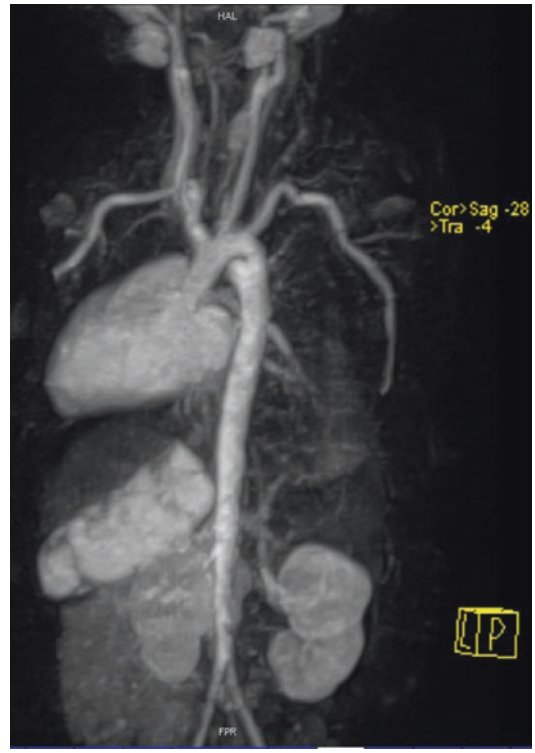

Fig. 15.8 MR angiogram of a child with EA/TEF and an incomplete double aortic arch (diverticulum of Kommerell)

completed with interrupted sutures and extraluminal knots (Fig. 15.6).

Even cases with an EA/TEF and a right-descending aorta can be corrected in the same fashion. Figure 15.7 demonstrates such a situation. In case of a double aortic arch, however, a left-sided approach should be discussed. Figures 15.8, 15.9, and 15.10 depict a child with an incomplete double aortic arch (diverticulum of Kommerell, [13, 14]), which had been approached from the left side to perform a primary repair.

If the primary anastomosis is under too much tension or tears have already happened, several techniques are available before aborting the primary repair. Myotomie, flaps and partial gastric pull-ups will be dealt with elsewhere. Before resorting to such techniques without adequate personal expertise, one may consider mobilizing the distal esophagus further down to the diaphragm. Moreover, a fine management of the sutures as described earlier may be helpful to gain extra length.

If the anastomosis must be aborted, the further management remains a matter of vivid discussion and certainly depends on several factors like the individual anatomy and associated malformations, the setting within the hospital, and the socioeconomic situation of the family. The lower segment should be closed with interrupted sutures and may be fixed to the vertebral column to avoid retraction. The upper segment may be closed completely as well or everted as a spit fistula.

Before closing the chest, some colleagues install an extrapleural chest drain in case the anastomosis leaks. Others place a chest tube only

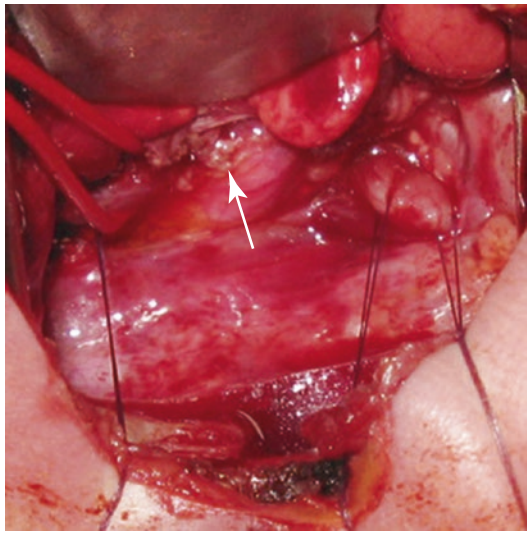

Fig. 15.9 The same child as in Fig. 15.8, approached from the left side (the anatomical aspect is mirrored). The TEF (at 9 o'clock) has been encircled with a vessel loop close to its junction to the trachea. A bulb of (pulsating) tissue crosses and encircle(s) the trachea, which is the incomplete double aortic arch. The upper pouch has been marked with two stitches

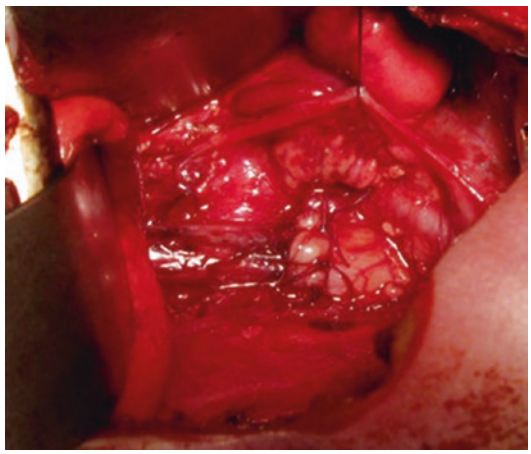

Fig. 15.10 Final anastomosis of this child

in "problematic cases" [15]. In neonates with a short-gap EA/TEF, we stopped doing so for three reasons. Firstly, the rate of anastomotic leaks is so small that many children would be drained in vain. Secondly, such a drain must be left in situ until the anastomosis has been investigated for patency, which usually takes place several days postoperatively. Finally, this drain may not necessarily reach a leak adequately, if it happens. Instead, we only close the muscles in several layers and refrain from suturing the intercostal space in order to avoid rib fusions.

Results, Issues, and Discussions of a Primary Repair

Many issues contribute to the postoperative course of any case with EA/TEF. Certainly, there are numerous nonsurgical factors like birth weight and age, delayed diagnosis, cardiac defects, associated malformations (e.g., VATER), and presence of genetic defects. On the other hand, specific operative details and complications influence the long-term sequelae significantly. Since this chapter focuses on technical aspects of a primary repair, we will focus the discussion on surgical issues and results. Theoretically, the postoperative complications may be divided into "form versus function," meaning "form" includes anastomotic leaks, strictures, and recurrent TEFs, while "function" comprises motility disorders, gastrointestinal reflux, and tracheomalacia. Some of these findings will influence the long-term quality of life of our patients significantly.

The rate of anastomotic leaks varies considerably in the literature. Just recently, Borruto et al. [3] published a meta-analysis about the outcome of thoracoscopy versus thoracotomy for EA/TEF repair. Their manuscript supplies an excellent overview of the present data and concludes that the rate of anastomotic leaks and strictures did not differ significantly between the two techniques (odds ratio of 0.56 in favor of the conventional open approach). But again we refer to Chap. 15 for a detailed discussion about this specific approach. Clinically, an anastomotic leak may occur in 5–25 % of cases [16]. Usually, it becomes apparent with signs of a systemic infection increase, saliva appearing in the chest tube, or the development of an emphysema. A radiological study of the anastomosis demarcates the defect [17]. Most minor leaks may be treated conservatively [16]. Drainage (Replogle suction

tube plus transanastomotic tube) and antibiotics contribute to a spontaneous healing within weeks. If major leaks occur, the adequate strategy should be considered with great care. An immediate operation should be driven by the essential question: What can we do better next time in order to avoid another leak? If tension and ischemia played a major role in the previous operation, there may be some doubt that these conditions have improved significantly. Furthermore, saliva and infectious material may have already damaged the esophageal tissue somehow. So an immediate intervention must always include a "plan B," i.e., the abortion of the primary repair as mentioned above.

Anastomotic strictures are quite common and multifactorial. At least 30% of the EA/TEF patients and up to 50% with pure EA require esophageal dilatations for anastomotic strictures [8]. Extensive mobilization and devascularization, an anastomosis under tension, postoperative leaks, and a significant gastrointestinal reflux may be surgical contributors [16]. Most strictures respond to bouginage or dilatation. Interestingly, there is no clear evidence in the literature, as to which procedure is more effective despite the frequency of stricture treatment [18]. We will deal with these issues in Chap. 15 again. In future, topical agents like mitomycin [19] may increase the efficacy of stricture treatment (see Chap. 33).

Compared to normal children, the incidence of a gastroesophageal reflux (GER) is considerably higher in children with an EA/TEF [20] and may necessitate a fundoplication in 32–30% of all cases [8]. Consequently, all patients should be investigated for a GER eventually (see Chaps. 36 and 37). Some of the causes for the GER may be attributed to the initial repair technique. It is well known that children with EA/TEF have an impaired esophageal motor function [21]. On the other hand, an extensive mobilization of the lower segment down to the diaphragm may weaken the intra-abdominal fixation of the GE junction or even cause a transposition the GE junction above the diaphragm. Furthermore, such extensive mobilization may compromise the vagal nerve fibers converging along the distal esophagus and could contribute to a motility disorder [22]. We will deal with the adequate management of GER in the next chapter.

Moreover, it should be mentioned that every case of EA/TEF may be associated with a certain degree of tracheomalacia. During the immediate postoperative phase, the spontaneous breathing may be impaired, especially when the child is fed orally, and the wide upper portion bulges into the membranous portion of the trachea. A stenosis or stricture of the anastomosis worsens this effect. Later in life, children with EA/TEF may present with a barking cough and inspiratory stridor. Cases of severe tracheomalacia must be investigated by tracheobronchoscopy. This investigation must be performed without a tracheal tube (stenting of the malacia) and during spontaneous breathing (negative pressure in the chest during inspiration provokes the tracheal collapse). Usually, significant tracheomalacia improves over time and up to 1 year. Hence, only severe cases with acute life-threatening events (ALTE) should be considered for aortopexy under bronchoscopic control [23]. Stenting should be the "last resort" option due to long-term consequences; for further information, we refer also to Chaps. 40, 41, and 42.

Finally, it must be noted that a contemporary study reported that no musculoskeletal sequelae were directly attributable to thoracotomy for EA/TEF repair [24]. So the open approach may not be out-fashioned yet? The long-term observation of Sistonen [25], who investigated the respiratory morbidity and pulmonary function of adults after repaired esophageal atresia as newborns, raises a major concern. He found that thoracotomy-induced rib fusions and gastroesophageal reflux were the strongest risk factors for restrictive ventilator defects [25].

In conclusion, we believe that a precise and experienced technique of a primary repair makes all the difference for patients with an EA/TEF concerning the postoperative complications and long-term quality of life.

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Thoracoscopic Repair of Esophageal Atresia and Tracheoesophageal Fistula

16

George W. Holcomb III

Introduction

The topic of esophageal atresia (EA), with or without tracheoesophageal fistula (TEF), will be covered in several chapters in this book. Therefore, this chapter will not reiterate information about etiology, classification, the open repair via thoracotomy, postoperative management or management of postoperative complications such as recurrent TEF, gastroesophageal reflux, or indications for aortopexy.

The primary focus of this chapter is to describe the thoracoscopic repair and to provide information regarding this approach. In addition, our institution is a training center for pediatric surgeons. As such, some of the issues that will be discussed relate to similar centers and may or may not be applicable in the private practice setting.

In 1999 during the IPEG Congress in Berlin, Drs. Thom Lobe and Steve Rothenberg (in concert with other surgeons) performed a thoracoscopic repair of a 3-month-old infant with isolated EA [1]. This infant recovered nicely, but did require several esophageal dilations. At the 2000 IPEG meeting, Dr. Rothenberg described the first thoracoscopic repair of an infant with EA/TEF [2]. This patient has continued to recover well without any significant complications. We performed our first thoracoscopic repair of an infant with EA/TEF on Memorial Day (late May), 2002. The operation also proceeded very nicely, and the patient recovered uneventfully without the need for dilation or fundoplication. Since that time, five of the six pediatric general surgeons in our group have either performed this operation or supervised this operation being performed by one of the pediatric surgical residents. Thus, at our institution, the thoracoscopic approach has become the favored approach for most babies with EA/TEF who do not have significant associated diseases.

Preoperative Evaluation

The preoperative evaluation for a baby undergoing a thoracoscopic repair is similar to the baby undergoing the traditional open approach. An evaluation for congenital cardiac anomalies is important, as is a sonographic study to evaluate the location of the aortic arch. Further radiographic evaluation for the VACTERL (vertebral, anorectal, cardiac, tracheoesophageal, renal, limb) anomalies is similarly needed as for the open operation.

The baby who is less than 2.5 kg is a challenge for the thoracoscopic approach. That is not to say

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that this baby should be excluded from undergoing a thoracoscopic repair by an experienced surgeon. However, what makes the operation easier in some babies, as compared to others, is the baby's weight (3 kg or greater), the lack of associated abnormalities, and, most importantly, a close proximity of the two esophageal segments. Therefore, it is my preference to pay close attention to the chest radiograph to see how caudal the upper pouch appears to extend. In addition, it is also my preference to perform bronchoscopy at the time of the thoracoscopic repair to identify the location of the TEF (Fig. 16.1). If the fistula is entering at the carina, the esophageal segments will be further apart than if the fistula enters the middle or lower trachea. Thus, the location of the TEF is helpful for anticipating where the fistula will be found in the chest at the time of the thoracoscopic repair.

This operation is not an emergency. It can be scheduled 2–3 days following birth in order to allow adequate time to perform the operation. In general, this is not an operation that should be performed beginning at 4 o'clock in the afternoon, but rather it is best performed starting earlier in the morning with one's regular operating crew. While awaiting operation, the baby should be turned onto his/her side to allow the oral secretions to drain out of the mouth rather than allow them to accumulate in the posterior pharynx and become aspirated. Also, it is important to have the Intensive Care nurses suction the baby's oropharynx at least every 2 h and more frequently if needed. The baby does not need to be intubated preoperatively unless the baby has respiratory symptoms. Management of the baby in respiratory distress is beyond the purview of this chapter and can be found in other literature reports [3–6].

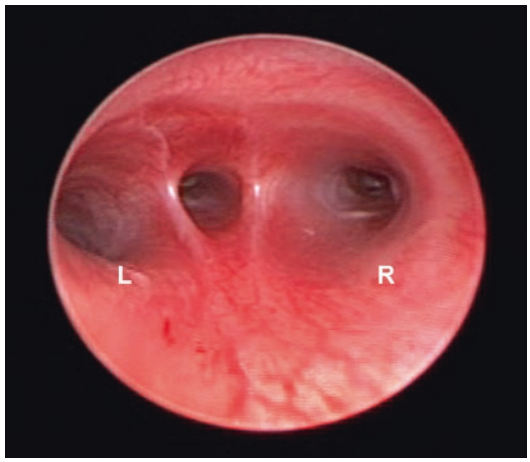

Fig. 16.1 Preoperative bronchoscopy allows the surgeon to confirm the diagnosis of esophageal atresia and tracheoesophageal fistula and also to better understand the expected gap length between the two esophageal segments. As seen in this baby, the fistula enters the carina which indicates that the surgeon should expect a relatively large gap between the two esophageal segments. A fistula that enters the mid-trachea would indicate that the two esophageal segments are likely closer together. (*R* right mainstem bronchus, *L* left mainstem bronchus)

Thoracoscopic Technique

The baby is transported to the operating room, and appropriate intravenous and, in some instances, intra-arterial access are established. As mentioned earlier, it is my preference to perform a preoperative bronchoscopy to identify the site of insertion of the distal TEF. Tracheal intubation, rather than left mainstem intubation, is generally utilized by most pediatric surgeons as the positive pressure pneumothorax will collapse the ipsilateral lung. Also, it can be difficult to perform left mainstem intubation in a small baby. If so desired, a variety of techniques are available to occlude the right mainstem bronchus such as tracheal intubation and placement of a bronchial blocker into the right mainstem bronchus.

In our early experience, we performed the operations with tracheal intubation and conventional mechanical ventilation. However, because of our status as a pediatric surgery teaching institution, we are also an anesthesia resident teaching center as well. As such, we have been dissatisfied with the use of conventional mechanical ventilation provided by the anesthesia residents. Therefore, we now prefer to perform these operations using tracheal intubation and the oscillating ventilator which will be discussed later.

Following intubation and initiation of appropriate ventilation, the baby is turned onto his/her left side (assuming a left aortic arch). The baby is turned more prone than lateral as the esophagus is a posterior mediastinal structure (Fig. 16.2).

Positioning the baby more prone allows the lung to fall forward and out of the area of visualization and dissection. The surgeon and camera holder stand at the front of the baby, and the scrub nurse is best positioned at the baby's back (Fig. 16.3). Following adequate prepping and draping, it is my preference to place an initial 5-mm port at approximately the eighth or ninth intercostal space in the posterior axillary line. It is through this port that a 45° or 70° 4 or 5 mm telescope is introduced. Following insertion of this cannula using a cut-down technique, a pneumothorax with carbon dioxide insufflation (1 L/min) to a pressure of 4–6 torr is created. There can be some initial desaturation as right-to-left shunting may occur. However, after a few minutes, this usually stabilizes. Our preference is to introduce the working instruments using the stab incision technique in the fourth and sixth intercostal spaces in the posterior axillary line just beneath the scapula. These are the two working ports for the surgeon. In our experience, and certainly with conventional ventilation, a fourth port instrument is often needed to help retract the lung. This fourth instrument is often inserted in the 10th or 11th intercostal space near the spine (see Fig. 16.2). A second assistant is sometimes needed to retract the lung using this instrument.

Following creation of an adequate pneumothorax and introduction of the instruments, the field of view is amazing, especially if this is the first time one is performing the operation thoracoscopically. Initially, our preference was to identify the proximal esophagus into which a red rubber catheter has been placed per os. If it is difficult to identify the proximal esophagus, the anesthesiologist is asked to manipulate the catheter and the proximal esophageal pouch can usually be identified. Usually, it is not as easy to identify the distal esophagus as in an open operation because the

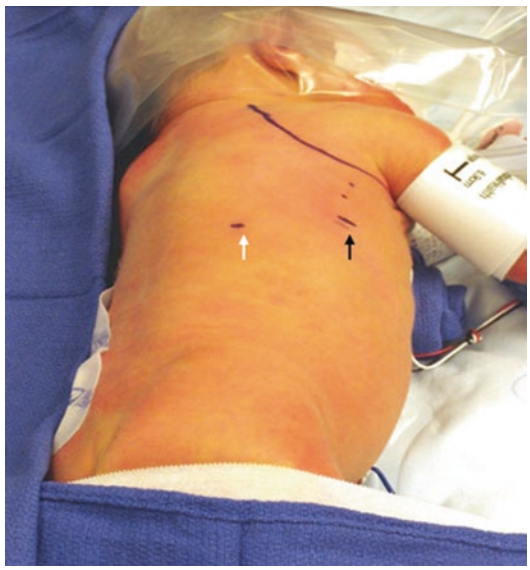

Fig. 16.2 As the esophagus is a posterior mediastinal structure, the baby should be turned more prone than lateral to allow the lung to fall forward and away from the area of visualization and dissection. On this newborn, the site for introduction for the initial 5 mm cannula is marked with a black arrow. Above it are two dots marking the stab incisions through which instruments will be inserted for use by the surgeon. On the left side, a final port is sometimes needed (*white arrow*) for lung retraction. With the use of the oscillating ventilator, this port is now often not needed. The lower border of the scapula has also been marked

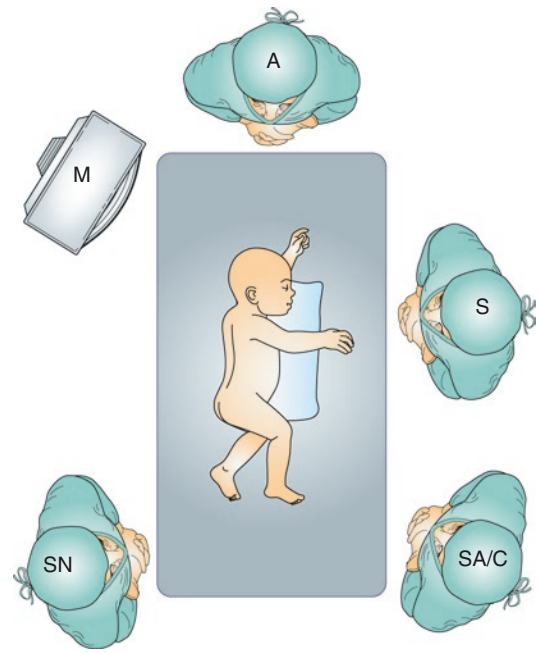

Fig. 16.3 The surgeon (*S*) stands at the front of the baby with the surgical assistant/camera holder (*SA/C*) to his/her left. The scrub nurse (*SN*) is usually opposite the surgeon at the level of the camera operator. The monitor (*M*) is situated opposite the surgeon for optimal viewing (*A* anesthesiologist) (From Holcomb et al. [7]. Reprinted with permission)

positive pressure pneumothorax often prevents ventilation through the fistula. As one's experience increases, it becomes easier to understand where the distal esophagus lies.

Our preference is to divide the azygos vein as the fistula is usually coursing just underneath it. If it is clear that the fistula enters the trachea cephalad to this vein, it may not be necessary to divide it. Assuming ligation and division of the vein is needed, this can be performed using the cautery, ultrasonic scalpel, or LigaSure (Covidien, Mansfield, MA), depending on one's preference. Initially, we utilized the LigaSure but now divide the azygos vein with cautery.

After the proximal esophagus is identified, attention is directed toward the distal esophagus. Blunt dissection initially begins at the level where the distal esophagus enters the trachea. Usually, there is no significant bleeding and hemostasis can be controlled with cautery. Our preference is to perform this dissection using the Maryland dissecting instrument, although other surgeons may prefer other instruments. Once the fistula is identified and mobilized, we next proceed to expose the proximal esophagus, again using a combination of blunt dissection with hemostasis controlled with cautery. It is important to remember that the wall of the proximal esophagus is quite sturdy as this structure has been obstructed for 7–8 months in utero. Sometimes little dissection of the proximal esophagus is needed, and sometimes more dissection is required, depending on the gap between the two esophageal segments. Assuming that a thoracoscopic repair is feasible, the distal TEF is then ligated using a variety of techniques. Initially, we utilized endoscopic stainless steel clips to ligate the fistula at the junction of the esophagus and the trachea (Fig. 16.4). The fistula is then divided distal to the second clip. Now, my preference is to use a Weck clip (Hem-o-lok, Teleflex Medical Inc., Research Triangle Park) as the stainless steel clips can erode through the fistula and may have contributed to a recurrent TEF in one case. (Others may not feel this is a concern.) Another possibility is to divide the esophagus at the level of the trachea with scissors and suture to close the resulting tracheal defect with interrupted 5-0 suture. Either absorbable suture or silk can be used for this purpose. We have utilized all of these techniques and found them satisfactory. If suture closure of the trachea is desired, either intracorporeal or extracorporeal knot tying can be utilized.

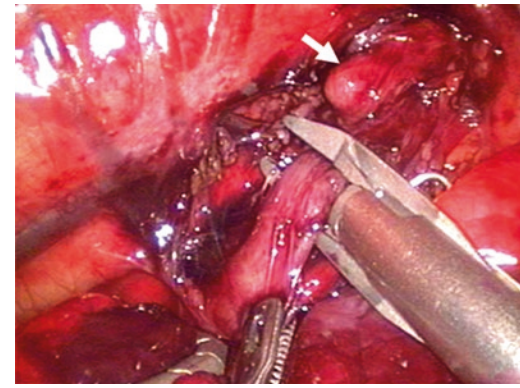

Fig. 16.4 This operative photograph depicts ligation of the fistula with stainless steel clips at the junction of the distal esophagus and trachea. A red rubber catheter is noted in the proximal esophagus (*arrow*)

After the distal esophagus has been disconnected from the trachea, the esophageal anastomosis is performed with 4-0 or 5-0 suture. Either absorbable (polyglactin or polydioxanone) or nonabsorbable (silk) sutures can be used. In a 2007 report from our institution, we looked at 99 patients and found that there was no difference in the incidence of anastomotic leaks or stricture with absorbable or nonabsorbable suture [8]. Initially, as there is usually some tension on the anastomosis, it may be helpful to secure the first two or three sutures using extracorporeal knot tying. As occurs with the traditional open operation, the back row of sutures is usually tied inside the lumen and the front row is tied with the knots on the outside. Prior to complete closure on the front side, our preference is to place a small (6–8 Fr.) Silastic tube through the baby's nose, through the anastomosis, and into the stomach (Fig. 16.5). This tube can be used for feeding purposes if desired in the postoperative period. Following introduction of this Silastic tube, the anterior row of sutures are then placed. If the surgeon does not feel that a good anastomosis has been performed, then conversion to an open operation is suggested.

Following completion of the esophageal anastomosis, the esophageal suture line and the

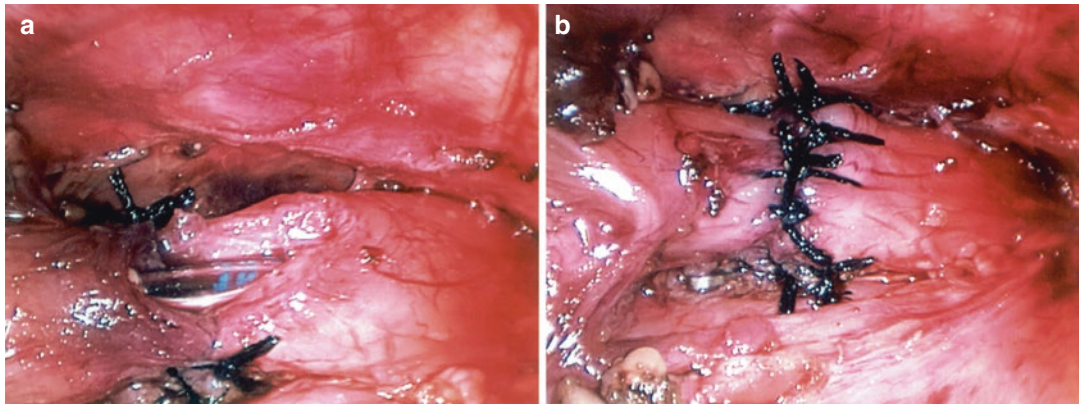

Fig. 16.5 *On the left* (**a**), after completing the posterior anastomosis, a soft 6-French tube is introduced through the infant's nares and is seen coursing through the esophageal anastomosis into the stomach. This is often helpful in the postoperative period for feeding. *On the right* (**b**), the anterior portion of the anastomosis has been completed with interrupted silk sutures which were tied intracorporeally (From Holcomb et al. [7]. Reprinted with permission)

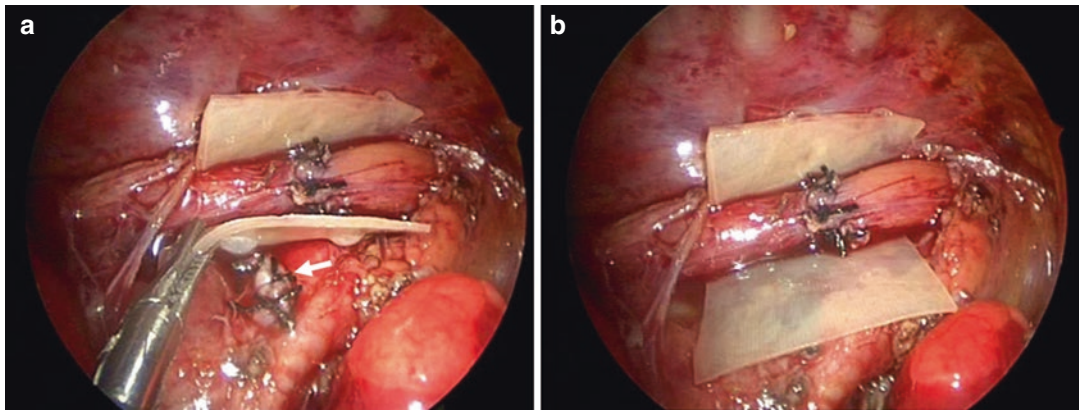

Fig. 16.6 After completing the esophageal anastomosis, it is important to try to separate the esophageal suture line from the fistula closure on the trachea (*white arrow*, **a**), if possible. Often these two sites align next to each other. We now interpose a piece of Surgisis between the two suture lines to separate them (**a**, **b**). We have not had a recurrent fistula develop after instituting this maneuver several years ago (From St. Peter et al. [9]. Reprinted with permission)

tracheal closure are often abutting each other. Our group reported a technique using Surgisis (Cook Inc., Bloomington, IN) which is positioned between these two suture lines to help prevent the development of a recurrent tracheoesophageal fistula (Fig. 16.6) [9]. With the open operation, it is sometimes possible to interpose either pleura or other soft tissue between the two suture closures. However, this can be quite difficult thoracoscopically and is the reason we often place Surgisis between the two suture closures.

The instruments are removed, and a soft Silastic drain is tunneled through one of the caudal incision sites and situated near the anastomosis. The lung is allowed to expand and the small incisions are closed with absorbable suture. Steri-Strips (3 M Corp., St. Paul, MN) are then placed, and the baby is transported to the neonatal unit.

The postoperative course for a thoracoscopic operation is no different than for the open approach. An esophagram is usually performed 5–7 days of the operation. If there is no evidence of leak, then oral feedings are initiated. If a leak is identified, it is managed as similarly described in other chapters. The remainder of the postoperative course is also described in other chapters.

Literature Report

There are a number of literature reports describing large experiences with the open operation for repair of EA/TEF [10–13]. Most of these reports are from the 1980s and early 1990s. The largest series of patients undergoing a thoracoscopic EA/TEF repair was reported at the 2005 meeting of the American Surgical Association [14]. This was a six-center report from three institutions in the United States and three institutions from three other continents. Management and outcomes in 104 babies were described. These patients had the usual associated VACTERL conditions with ten having greater than two VACTERL anomalies. In this series, an anastomotic stricture (defined as a stricture on the initial esophagram) was found in four babies (3.8 %). An anastomotic leak was seen on the initial esophagram in seven babies (6.7 %). The operation was converted in five babies for the following reasons: right aortic arch (1), intraoperative desaturations and a long gap between esophageal segments (3), and too small in size, i.e., 1.2 kg (1).

Regarding associated conditions, ten babies had imperforate anus and four had duodenal atresia. Five babies required cardiac repairs other than a VSD or ASD closure. Twenty-six babies (25 %) needed fundoplication and seven required an aortopexy of which six were performed thoracoscopically. Two recurrent TEFs developed. One occurred at 3 months postoperatively, and one developed at 8 months following the initial operation. Three babies died, but none of these were related to the operative approach. One baby died at 7 months following an episode of necrotizing enterocolitis which was attributed to drinking herbal tea; one baby had undergone successful thoracoscopic EA/TEF repair, but died of congenital heart disease prior to cardiac repair; and one baby was recovering nicely, but died at 20 days of life when the esophagus was inadvertently intubated and the anastomosis was disrupted. This baby died within 24 h of this event. Comparison of the results from this thoracoscopic report and a number of large series of open operations from the United States is seen in Table 16.1.

Table 16.1 A comparison of a large series of babies undergoing thoracoscopic repair of EA/TEF compared with four large series using the open approach

	Multi-institutional six-center thoracoscopic study [14]	Engum et al. (1971–1993) [10]	Spitz, Kiely (1980–1984) [13]	Randolph et al. (1982–1988) [12]	Manning et al. (1977–1985) [11]
Number of patients	104	174	148[a]	39	63
Mean length of hospitalization (days)	18.1 (6–120)	N.R.	N.R.	N.R.	24 (9–174)
Anastomotic leak	7.6 %	N.R.	21 %	10.2 %	17 %
Anastomotic stricture	3.8 %[b]	32.7 %[c]	17.7 %	33.3 %	4.3 %[d]
Patients requiring at least one dilation	31.7 %	32.7 %	N.R.	33.3 %	N.R.
Anastomotic revision	1.9 %	0.9 %	2.7 %	5.1 %	N.R.
Fundoplication	24.0 %	25.2 %	18 %	15.3 %	16.9 %
Aortopexy	6.7 %	N.R.	16 %	N.R.	4.7 %
Mortality					
Related to EA/TEF repair	0.9 %	4.5 % (overall)	14.8 % (overall)	0 %	3.1 %
Not related to repair	**1.9 %**			**7.6 %**	**11.1 %**
	2.8 %			7.6 %	14.2 %
Recurrent fistula	1.9 %	2.2 %	12 %	5.1 %	6.4 %

N.R. not reported
[a]87 % are Gross Type C
[b]Stricture is defined as a significant narrowing on the initial esophagram
[c]Stricture in this paper is defined as requiring >4 dilations
[d]Stricture in this paper is defined as requiring >2 dilations

Modifications in the Approach

As mentioned, our group has described interposing Surgisis between the esophageal and tracheal closures to help prevent a recurrent fistula [9]. Also, over the past 3 years, our group has begun to utilize the oscillating ventilator as the primary mode of ventilation in these babies (Fig. 16.7) [16]. This has evolved for two reasons. First, as mentioned, it takes the oxygenation and ventilation out of the hands of a resident anesthesiologist. Also, there is no longer concern for hypercarbia. The babies are intubated in the operating room and placed on the oscillating ventilator which is controlled and managed by one of our respiratory therapists. Assuming a 3–3.5 kg healthy baby, the standard settings are a mean airway pressure of 13–15 and an FiO_2 of 70 %. The FiO2 can usually be weaned after 10–15 min. If the baby is shaking too much, the Hertz can be reduced from the initial 11–13 setting to 8–9. The use of the oscillator is advantageous in a surgical residency training program because the operative time is not as important. Early in our experience, it became evident that the operation needed to be performed in 2–2.5 h due to the development of hypercarbia and inflation of the lung. Now, the need to perform the operation expeditiously is not as important with the use of the oscillator. This has markedly improved the ability of our residents to participate significantly in these cases.

The main limitation in the use of the oscillator is the shaking of the baby. However, after 5–10 min, the surgeon becomes accustomed to this movement. In our experience and in discussion with our residents, the baby's shaking is not felt to be a significant limitation in performing the operation.

Fig. 16.7 Over the past 3 years, our group has begun to utilize the oscillating ventilator for ventilation in these babies. This photograph shows the baby turned on her left side and the endotracheal tube connected to the oscillating ventilator

Getting Started

One of the main limitations in the use of this approach is a surgeon's reluctance to begin an operation thoracoscopically with the fear of not being able to complete it. The best advice is to pick the first patients well. The optimal first or second baby should have a weight greater than 3 kg, no other associated anomalies, a left aortic arch, and a relatively low-lying proximal esophageal pouch (Fig. 16.8). Assuming that one can perform advanced laparoscopic operations (especially fundoplication as this involves intracorporeal suturing), the surgeon should discuss the thoracoscopic approach thoroughly and honestly with the parents. The surgeon should be encouraged to begin the operation thoracoscopically and proceed as far as he/she feels comfortable. If one is able to accomplish ligation of the fistula, but feels uncomfortable with the anastomosis, then conversion to an open procedure is very reasonable. However, one should believe in the benefits of the operation and not be concerned if conversion is necessary, as conversion implies good operative judgment rather than a failure in technique. Also, after the two esophageal segments have been mobilized, if the gap is too long, then conversion to an open operation is recommended in order to achieve a good outcome.

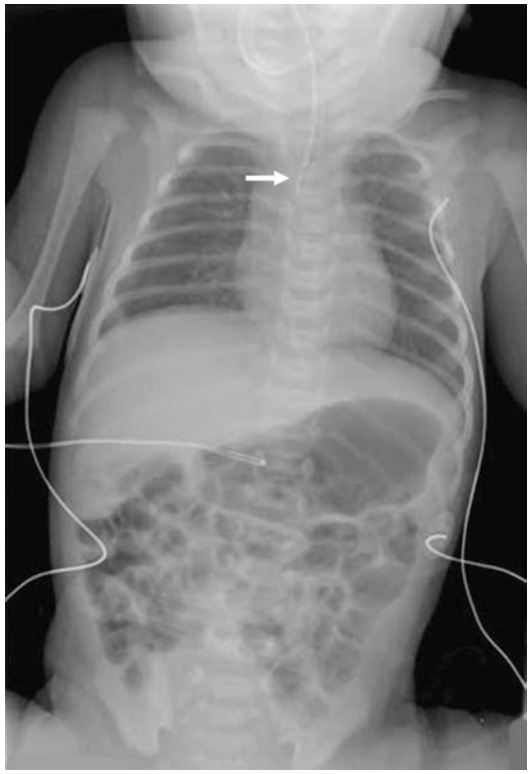

Fig. 16.8 This chest radiograph shows a baby with esophageal atresia and tracheoesophageal fistula. Note the relatively low-lying proximal esophageal pouch (*arrow*). This location of the proximal esophagus would be favorable for attempting thoracoscopic repair

Why Thoracoscopy?

The thoracoscopic approach for EA/TEF repair represents a natural evolution in the development of minimally invasive surgery in babies and children. This was certainly the last of the major pediatric surgery operations to be performed using a minimally invasive approach. In a number of surgeons' hands, this is a very reasonable approach and the outcomes are as good as with the open operation. The primary advantage is a reduction in musculoskeletal sequelae. In a 1985 report, a number of musculoskeletal problems were found in patients who had undergone an open thoracotomy for repair of esophageal atresia and fistula [17]. Similar reports in that decade and in the 1990s have confirmed the fact that musculoskeletal sequelae definitely occur following thoracotomy in infants [15, 18–20]. Advocates of the "muscle-sparing" open approach believe that the incidence of these subsequent problems is minimal [21]. However, although conceptually it certainly appears that this is true, there is a paucity of support in the literature.

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Repair of Other Congenital Esophageal Anomalies

17

Shawn D. St. Peter

Esophageal Duplications

Esophageal duplication cysts are unknown lesions, with an approximate incidence of 1 in 10,000 [1]. They account for about 20 % of all gastrointestinal duplications [2]. Because of the reported association of esophageal duplications and esophageal atresia (EA) [3, 4], some authors have sought a possible commonality in the embryogenesis of these defects. When rats were given Adriamycin to develop EA and tracheoesophageal fistula (TEF), 25 % also developed esophageal duplications [5]. This finding implies that esophageal duplications arise from the foregut, and failure of the esophagus to normally separate from the notochord may contribute to their development. It has also been postulated that esophageal duplications and bronchogenic cysts share a common origin [6]. However, esophageal duplications are histologically distinct from bronchogenic cysts by having layers of smooth muscle and being lined by gastrointestinal epithelium. Most duplications are cystic and do not share a common wall with the esophagus.

While many of these lesions are detected in childhood, up to one-third are found after age 12 [7]. The majority of these lesions are located near the esophagus or trachea [6, 8]. Chest or back pain, respiratory symptoms, or dysphagia are the more common presenting symptoms. Most patients present in infancy or early childhood [9]. The presentation may be more dramatic if the lesion becomes infected, including one report of an esophageal duplication masquerading as empyema [10]. Prenatal diagnosis by ultrasound (US) has also been reported [9, 11].

Esophageal duplications can usually be seen on plain films of the chest [6]. Computed tomography with IV contrast or magnetic resonance imaging (MRI) should be obtained preoperatively to delineate the three-dimensional position of the lesion relative to the trachea, esophagus, and vascular structures in the mediastinum (Fig. 17.1). Usually, the preoperative imaging will not be able to differentiate a bronchogenic cyst from a foregut duplication, but imaging studies may suggest a neurenteric cyst. The abdomen should be imaged as well as these neurogenic cysts can extend into the abdomen or be associated with a concomitant abdominal lesion [2, 8]. In a patient with spinal dysraphism and a newly identified mediastinal lesion, a neurenteric cyst should be considered [6]. In these cases, or when there is concern about a posterior mediastinal lesion, an MRI is recommended to evaluate for communication to the spinal column [12]. Endoscopic US has been described in adults for diagnosis by identifying several muscle layers in

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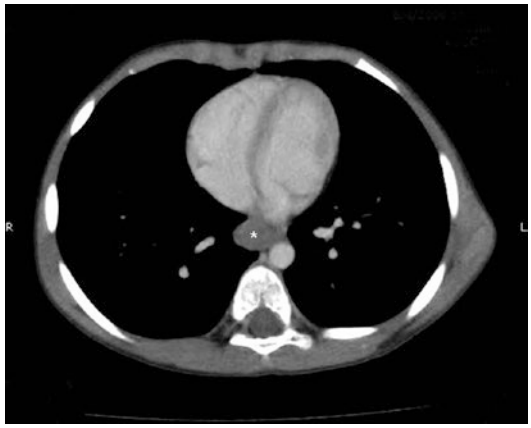

Fig. 17.1 This CT scan in an 8-year-old shows a foregut duplication cyst (*asterisk*) adjacent to the esophagus. The lesion measured 2×1.5 cm. The patient subsequently underwent right thoracoscopy with resection of the lesion (From Holcomb et al. [56]. Reprinted with permission)

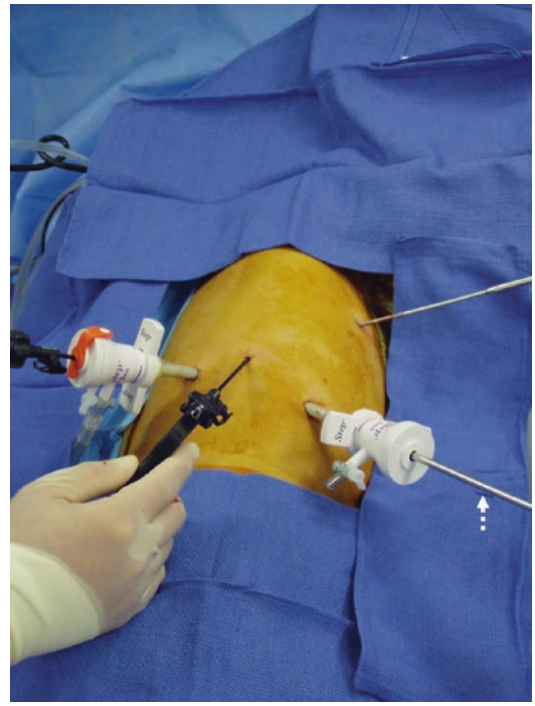

Fig. 17.2 The location of the ports for a right thoracoscopy and resection of the duplication cyst that is seen in Fig. 17.1 are depicted. As is evident, two 5 mm ports and two stab incisions are used. The uppermost stab incision is used for insertion of a diamond-shaped retractor. The *dotted arrow* identifies the camera port (From Holcomb et al. [56]. Reprinted with permission)

the cyst wall [13]. However, not all esophageal duplications possess a muscular wall. Endoscopic US may also identify the presence of esophageal communication, but this imaging modality is not available in many pediatric centers.

Ladd initially proposed cyst marsupialization and mucosal obliteration, but there is a substantial recurrence rate from this approach [6, 14, 15]. Also, although successful cyst aspiration has been described [13], recurrence after aspiration should be expected because of the epithelial lining [16]. Thus, optimal treatment of these lesions is complete resection.

There is debate in the literature about the role of observation in asymptomatic lesions in older patients. Some authors have suggested that observation is appropriate when the diagnosis is confirmed by aspiration in the asymptomatic patient [17, 18]. The cyst aspirate may be yellow colored, and/or clear, or turbid with leukocytes, macrophages, high sodium and chloride levels, and a low protein level [17–19]. Malignant degeneration in the forms of squamous cell carcinoma, adenocarcinoma, and rhabdomyosarcoma have been reported [20–26]. The relatively impressive number of reports of malignancy should be given heavy consideration, especially since there are a small number of esophageal duplications which have been followed long term. Additionally, these lesions can become infected, erode into surrounding structures, ulcerate which leads to hemorrhage, or become densely adherent within the mediastinum, all complicating subsequent resection [6, 10]. More serious complications have been documented in older patients, further arguing for resection as the preferred management strategy [6]. Therefore, most authors, including our group, recommend complete resection of all lesions at diagnosis [6–8, 12, 24].

Thoracoscopy is the preferred approach for resecting most foregut duplications. The instrument and personnel setup and operative plan must be tailored to the size and location of the lesion (Figs. 17.2 and 17.3). While posterior mediastinal lesions may benefit from a modified decubitus position and turning the patient more anteriorly (as is done for thoracoscopic repair of

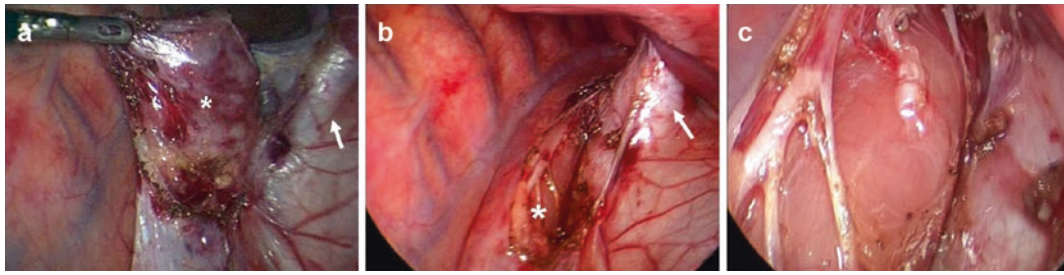

Fig. 17.3 Excision of an esophageal duplication cyst adjacent to the lower esophagus is depicted. (**a**) The cyst (*asterisk*) is being retracted away from the posterior lying esophagus. (**b**) The esophagus is identified (*asterisk*) after the cyst has been excised. In (**a**, **b**), the inferior pulmonary vein is marked with an *arrow*. (**c**) The wall of the esophagus is inspected, and the branches of the vagus nerve are seen as they course along the lateral wall of the esophagus. Histologic examination of the specimen revealed it to be an esophageal duplication cyst (From Holcomb et al. [56]. Reprinted with permission)

EA/TEF) [27], when the lesions are adjacent to large vessels, ready access by emergent thoracotomy must be considered. Additionally, duplications abutting the esophagus should be approached with adequate triangulation to repair an opening in the esophagus that might occur due to dense adherence of the cyst and the esophagus. Placement of a bougie in the esophagus can aid in palpating and identifying the esophagus. Also, it is helpful to locate the vagus and phrenic nerves early in the operation. Sometimes, decompressing the cyst can help to expose the planes of dissection [12]. Even lesions that are resected intact will often need to be decompressed to allow for extraction [28]. We have found that leaving the cyst intact is useful early in the operation to orient the surgeon as to the location of the relevant structures, followed by cyst decompression to complete the dissection around the sides and back of the lesion, which may otherwise be difficult to expose. Some authors have argued against a thoracoscopic approach when the cyst produces mediastinal shift [29]. However, we feel these lesions can be decompressed preoperatively or during the operation to allow for thoracoscopic resection. Lesions along the inferior esophagus may be easier to expose and resect from a laparoscopic approach if they invade the esophageal hiatus or have intra-abdominal extension (Fig. 17.4). The general setup and operative plan utilized for laparoscopic fundoplication or esophagomyotomy procedures provide an excellent view of this area in these cases.

If there are signs of infection preoperatively, it may be prudent to manage these lesions in a staged sequence with either needle aspiration or thoracoscopic decompression followed by interval resection after a course of antibiotics [8, 30]. Although there are no clear recommendations for the timing of definitive surgery, we have used a 2-month interval for infected cysts with good success.

Congenital Esophageal Stenosis

Congenital esophageal stenosis (CES) is a rare lesion manifesting as a discrete, intrinsic, segmental stenosis causing obstruction of the normal aboral propulsion within the esophagus. These unusual lesions occur in 1 in 25,000–50,000 live births [31]. There are three generally accepted types of stenoses: fibromuscular stenosis, mucosal membranes or webs, and tracheobronchial remnants. Tracheobronchial remnants appear to be the most common form, representing about three-fourths of cases with the fibromuscular type compromising most of the remainder [32, 33].

Symptoms usually begin early in life. In a review of the published literature, the mean age of documented symptomatology was 3.2 ± 4.5 months [34]. However, the mean age at treatment was 2.6 ± 3.0 years which underscores the difficulty in identifying these lesions as the source of symptoms. Initial barium swallow studies may not show the lesion in the neonatal

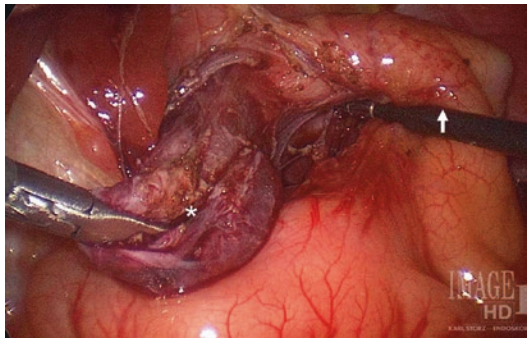

Fig. 17.4 This intraoperative photograph shows an esophageal duplication cyst (*asterisk*) being excised from the lower mediastinum utilizing a laparoscopic transhiatal approach. Notice the intra-abdominal esophagus (*arrow*) being retracted laterally

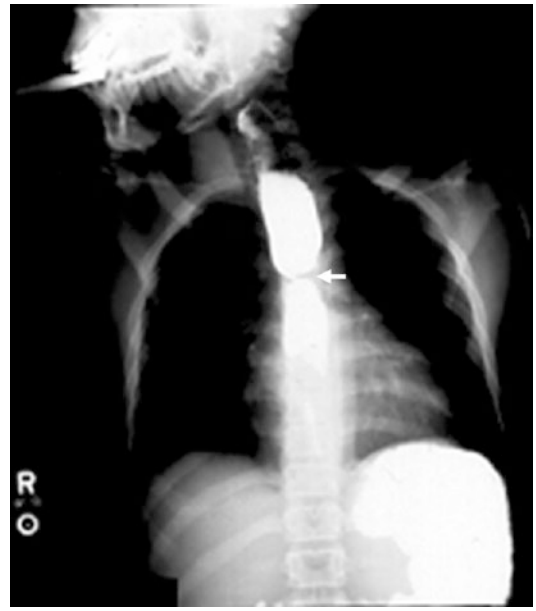

Fig. 17.5 This child presented with significant dysphagia and weight loss. An esophagram revealed marked narrowing of the mid-esophagus (*arrow*) due to congenital esophageal stenosis. This child underwent resection of the stenosis and primary repair of the esophagus (From Holcomb and Murphy [55]. Reprinted with permission)

period [35]. Symptoms include regurgitation, dysphagia, failure to thrive, hypersalivation, recurrent aspiration or respiratory tract infections, and food or foreign body impaction. There is an association between CES and EA that has been long recognized [36–40]. A review of 25 patients with CES and another congenital anomaly documented 15 of these patients also had EA [34]. When considering newborns known to have EA, the estimated incidence of a concomitant CES has been found to be as low as 0.4 % and as high as nearly 10 % [36–38], making these lesions an important consideration in babies with swallowing difficulties after EA repair. One group found that biopsy of the tip of the distal esophagus may help in the diagnosis as histologic abnormalities in the esophageal wall might be consistent with congenital stenosis [37]. The incidence of CES has been found to be higher with pure EA than with EA/TEF [37].

The diagnosis is often initially suspected on a contrast swallow study which is the primary diagnostic tool (Fig. 17.5). With rare exception, the lesion will be identified in the distal portion of the esophagus [34]. The stenosis on the esophagram may either be abrupt or tapered [33]. While it has been postulated that an abrupt stenosis more likely represents tracheobronchial remnants and a tapered stenosis indicates the fibromuscular type, these relationships are not consistent [41]. The precise etiology of the stenosis can rarely be made prior to histologic evaluation after resection. In a majority of published cases, the preoperative diagnosis was not CES, but achalasia or peptic stricture [34]. Cartilaginous tissue can be seen on endoscopic US which may be a promising future adjunct in separating tracheobronchial remnants from fibromuscular disease [42, 43].

Endoscopic dilation has become the standard management for mucosal webs, and some authors have found it to be successful with the fibromuscular type as well [35, 38, 42]. Others continue to recommend excision with end-to-end anastomosis when the tracheobronchial remnant form is present as this type is often refractory to dilation [34, 41]. Moreover, there may be a higher rate of esophageal perforation with dilation in these patients [34, 44]. Unfortunately, a selective approach based on the type of stenosis is currently not feasible due to the inability to reliably diagnose the type of lesion prior to histologic confirmation. Therefore, fluoroscopically guided balloon dilation has been recommended as the initial therapeutic maneuver in all patients with CES

by several authors [33, 37, 41]. The threshold for proceeding with resection varies among series with several authors recommending resection when symptoms persist after three dilations [35, 38, 40, 42]. Longitudinal myotomy with fundoplication has been reported for distal fibromuscular lesions [38, 42]. Perhaps endoscopic US may facilitate decision-making by identifying cartilage in the stricture as this imaging modality becomes more common in the pediatric population.

The role of gastroesophageal reflux and the potential need for an anti-reflux procedure in patients requiring resection of CES should be considered. An anti-reflux operation is recommended when the gastroesophageal junction is involved in the resection and repair [45–47]. In patients with EA, some authors have recommended the routine performance of an anti-reflux operation at the time of the initial dilation of CES [35, 37, 48]. When fundoplication is considered, some authors prefer partial wrap may be appropriate due to the concern about esophageal dysmotility [37].

Anastomotic Strictures

The most common complication after repair of EA is the development of a stricture at the anastomosis. A large consecutive series has documented the need for at least one dilation in 40 % of the patients [49]. The type and size of suture utilized in the esophageal repair have not been shown to be a factor on the stricture rate [49]. The degree of tension is linearly related to the risk of stricture and is the most powerful patient variable influencing this complication. The presence of a postoperative anastomotic leak substantially increases the risk of stricture formation. Gastroesophageal reflux has also been implicated as a risk factor.

Endoscopic dilation is the initial therapy and is often all that is required. The mean number of dilations required in EA patients who require a dilation is approximately three dilations per patient [49]. There are little comparative data to definitively delineate the best mode of dilation. We currently use radial balloon dilation under

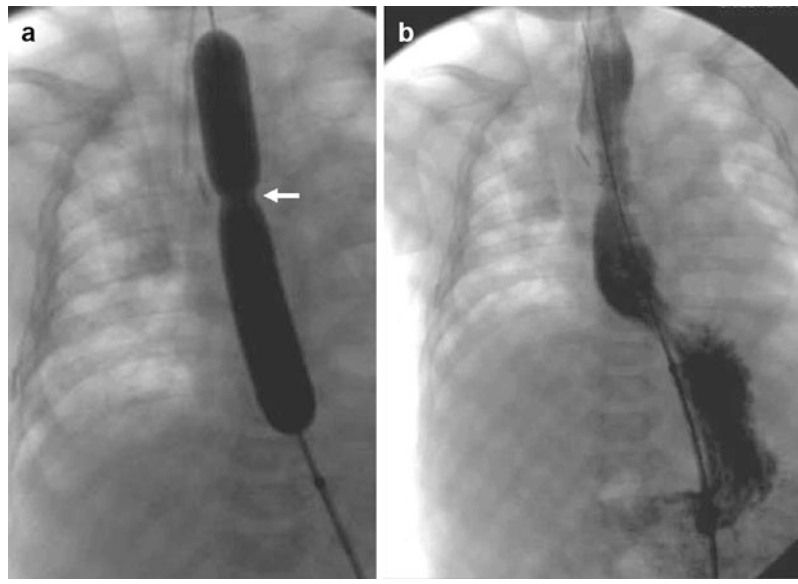

Fig. 17.6 On the *left* (**a**), this fluoroscopic image of a baby undergoing radial balloon dilation of an esophageal stricture following thoracoscopic repair of EA/TEF shows a waist (*arrow*) which identifies the most significant part of the stricture. On the *right* (**b**), an on-table esophagram was performed following radial balloon dilation of the esophageal stricture by injecting contrast material through a red rubber catheter with the patient positioned in reverse Trendelenburg. This study was performed in the patient depicted in (**a**). An esophagram in the operating room allows for assessment of the degree of esophageal dilation and assurance that esophageal perforation did not occur during the dilation

fluoroscopic guidance which offers the ability to clearly see the length of the stricture as well as the degree of narrowing prior to fully deploying the balloon (Fig. 17.6a). The responsiveness of the stricture to sequential dilation also offers some insight as to its stiffness. This author utilizes the fluoroscopy to perform an on-table esophagram after dilation and prior to leaving the operating room to evaluate for an iatrogenic perforation and to gauge the immediate success of dilation. This on-table study is performed by injecting contrast through a red rubber tube with the patient positioned in reverse Trendelenburg (Fig. 17.6b).

Recalcitrant EA strictures pose substantial challenges to the pediatric surgeon as there are no clear guidelines for the number of dilations that should be attempted prior to considering stricture resection or esophageal replacement. Topical mitomycin C has been employed in an attempt to reduce collagen synthesis and deposition after dilation [50, 51]. Similarly, injection or application of corticosteroid has been tried to prevent recurrent scarring after dilation [52–54].

Once the stricture is felt to be unsalvageable with dilation, considerable thought should be given to whether the patient is more likely to have success with focal stricture resection or with esophageal replacement.

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18 Evaluation and Repair of Laryngotracheoesophageal Clefts

Katherine K. Hamming and Frank L. Rimell

Introduction

A laryngotracheoesophageal cleft (LTEC) is a fissure between the laryngotracheal and pharyngoesophageal systems. The incidence is currently estimated to be 1:10,000 to 1:20,000 births and is increasing as less severe clefts are more often recognized [18]. Laryngeal clefts are more common in male children, with a male to female ratio of 5:3. Sixty percent are associated with other congenital abnormalities, most commonly tracheoesophageal fistula and tracheomalacia [12].

While severe clefts present with early significant pulmonary compromise and gross aspiration, a high index of suspicion is necessary to diagnose less severe clefts and prevent chronic pulmonary aspiration. Early diagnosis decreases morbidity and mortality. Laryngeal clefts are often associated with tracheoesophageal fistulas and esophageal atresia. Clefts can be associated with syndromes, such as Opitz-Frias and VACTERL [15].

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Embryology

There are several theories of esophageal and tracheal embryogenesis. In the classic theory, the larynx develops from the endoderm of the foregut and the mesenchymal elements from the fourth and sixth branchial pouches. Lateral ridges form on the lateral walls of the foregut and fuse in the midline in a caudal to cranial direction. This fusion forms the tracheoesophageal septum. Arrest in this fusion causes a laryngeal cleft, and the earlier the arrest, the more severe the cleft. However, this theory does not explain the origin of more common anomalies, such as tracheoesophageal fistula.

A second theory suggests that development of the trachea and esophagus occurs with a size reduction of the foregut that results in a system of folds of the foregut. A caudal fold develops in a cranial direction, and two cranial folds develop in a caudal direction. This theory is complemented by the idea that the trachea evolves as an outpouching of the ventral foregut.

In a third theory, the mesenchyme located between the digestive and respiratory systems (tracheoesophageal septum) is present initially, and the trachea descends from this tissue. Apoptotic epithelial cells have been found at the tracheoesophageal separation point, supporting an apoptotic phenomenon as part of the development of the trachea and esophagus.

Furthermore, several theories have been proposed to explain the development of tracheoesophageal abnormalities. One is intraembryonic pressure. The curvature of the cervical spine and

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development of the heart cause a displacement of the esophagus under tension. The second theory is epithelial occlusion. During development, there is a solid esophageal stage. If recanalization stops, anomalies persist. The third theory is vascular occlusion, leading to vascular insufficiency of some tissue. The fourth theory is differential cell growth, in which developmental cells dysfunction, causing anomalies [12].

Anatomy/Normal Function

The larynx is a complex, multifunctional organ which, when operating correctly, directs air in and out of the trachea and food into the esophagus. This structure allows for the complex functions of breathing, swallowing, and voicing. The trachea and esophagus are separated by the tracheoesophageal septum, which superiorly includes the posterior lamina of the cricoid cartilage and the paired arytenoids cartilages. For breathing, the arytenoids cartilages abduct, allowing the vocal cords to open and air to flow through. For eating, the arytenoids cartilages adduct, closing the vocal cords to protect the trachea from food or liquid. Normally, there is approximately 3 mm of tissue in the interarytenoid area superior to the level of the true vocal cords. However, in the case of a LTEC, the interarytenoid area or posterior larynx and trachea are deficient, and the depth of this cleft determines the severity of symptoms.

Classification

The most commonly used classification system is the Benjamin and Inglis system [1], which describes four severities of cleft, types 1–4. In a type 1 cleft, a supraglottic interarytenoid cleft extends to the level of the true vocal cords. A type 2 cleft extends below the vocal cords into the upper cricoid cartilage. A type 3 cleft extends through the cricoid cartilage and possibly into the cervical trachea, and a type 4 cleft extends into the thoracic trachea and extends variably toward the carina [1]. A modification of this classification system has been published by Rutter and includes five severities, with a type 5 that extends to or beyond the carina [15]. Sandu and Monnier have subdivided the Benjamin and Inglis system in the following way: type 3a is a total cricoid cleft, type 3b is a total cricoid cleft with extension into the posterior tracheal wall to but not beyond the sternal notch, type 4a extends to the carina, and type 4b involves one of the mainstem bronchi [16].

Presentation

The presentation of laryngotracheoesophageal clefts is variable and is dependent on the severity of the cleft. Children with mild type 1 clefts may be asymptomatic, whereas children with type 4 clefts present with severe respiratory distress at birth due to direct spillage of esophageal contents into the trachea and lungs.

Some patients with type 1 laryngeal cleft are asymptomatic and do not require treatment. Others may present with stridor, hoarse cry, or recurrent pneumonia. The child may have swallowing difficulty as evidenced by cough, dyspnea, or cyanosis during feeding. Aspiration is reported in 59–90 % of type 1 laryngeal clefts. A high index of suspicion is required for diagnosing a type 1 laryngeal cleft, and the differential diagnosis includes tracheoesophageal fistula, laryngomalacia, laryngeal mobility disorder, gastroesophageal reflux, and central neurogenic swallowing disorders.

One hundred percent of types 2, 3, and 4 laryngeal clefts have aspiration due to the communication between the esophagus and trachea. Type 2 clefts will present with symptoms of aspiration and recurrent pneumonia, typically more pronounced than type 1 clefts [11]. Types 3 and 4 laryngeal clefts present with early severe respiratory distress with bronchial flooding and difficulty maintaining ventilation.

Associated Syndromes and Malformations

Laryngotracheoesophageal clefts are associated with other congenital abnormalities in 58–75 % of cases [12, 13, 17]. The majority of these are

gastrointestinal anomalies and include esophageal atresia, tracheoesophageal fistula, imperforate anus, false rotation or failure of intestinal rotation, meconium ileus, and microgastria.

In a study of 74 patients with type 1 or 2 laryngeal clefts, Rahbar found multiple congenital anomalies in three patients. The diagnoses included fetal alcohol syndrome, trisomy 21, and CHARGE [14].

Kawaguchi et al. [9] studied nine patients with clefts involving the entire trachea or extending into the mainstem bronchi. They found that all nine had severe gastroesophageal reflux, six of nine had microgastria, two of nine had Meckel's diverticulum, two of nine had intestinal malrotation, and two of nine had abnormally enlarged left lobe of the liver.

Patients with LTEC can also have genitourinary anomalies, including hypospadias, kidney malformation, inguinal hernia, or testicular ectopia. Cardiac anomalies include coarctation of the aorta, transposition of the great vessels, patent ductus arteriosus, and ventricular septal defect. Reported craniofacial anomalies are cleft lip and palate, choanal atresia, micrognathia, glossoptosis, hypertelorism, dysmorphia, and anomalies of the external ear. And tracheal, bronchial, and pulmonary anomalies include short trachea, bronchial or tracheal stenosis, and abnormal lung separation or hypoplasia.

These associated anomalies are sometimes part of an associated syndrome. Syndromes associated with LTEC include G syndrome or Opitz-Frias syndrome, Pallister-Hall syndrome, VACTERL association, and CHARGE syndrome.

Patient Evaluation

In a patient with breathing or swallowing difficulties, initial workup may involve chest radiograph, speech therapy, swallow evaluation, or swallow study. A chest x-ray may show evidence of aspiration pneumonia. A contrast video swallow study will show immediate passage of barium into the trachea, but tracheoesophageal fistula and LTEC can be difficult to distinguish.

The diagnosis of laryngeal cleft is made with microlaryngoscopy and rigid bronchoscopy. The vocal cords, supraglottis, and trachea are topically anesthetized with lidocaine. A rigid telescope or bronchoscope is advanced through the larynx through the vocal cords and into the trachea to examine for other anomalies. Suspension laryngoscopy can be performed for better visualization and measurement of the cleft. The presence of a laryngeal cleft is examined by palpation of the interarytenoid space with a laryngeal probe or end of the bronchoscope. Instruments for measurement of the depth of the cleft are available [2]. It is important to perform a full airway evaluation, due to the high rate of synchronous anomalies in 50–60 % of cases [12].

Further, once a laryngeal cleft is diagnosed, systematic workup of other associated anomalies is necessary, including genetics consultation, cardiac ultrasound, renal ultrasound, and spine radiographs [5]. Given the frequency of multiple anomalies in children with LTEC, a multidisciplinary approach is necessary.

Treatment

Treatment of most laryngeal clefts is surgical. However, in a mild type 1 laryngeal cleft, medical management should first be optimized, including treatment of reflux and thickening feeds. If the patient is not aspirating with thickened feeds and is gaining weight appropriately, medical management may suffice.

Many patients with laryngeal cleft present with some degree of airway compromise due to aspiration of gastric secretions. A tracheostomy is necessary for most severe laryngeal clefts. A G-tube is also often necessary, as the baby will not be able to be fed orally for some time. Oral stimulation is important during the period of G-tube feeding to help minimize oral aversion once the patient can eat.

Many children with LTEC have congenital syndromes or associated comorbidities. These should be worked up and prioritized with a multidisciplinary approach.

Surgical repair of laryngeal clefts is performed through either an endoscopic or open approach. Endoscopic repair is indicated for type 1 and some type 2 clefts. There have been reports of

endoscopic repair of type 3 clefts [3, 13]. Described techniques include incision with cold steel or CO2 laser in the interarytenoid area, development of anterior and posterior tissue flaps, and placement of sutures to create a few millimeters of tissue in the interarytenoid area above the true vocal cord level.

A more recent technique for type 1 laryngeal clefts is injection laryngoplasty. Various materials have been used, including Gelfoam, Radiesse Voice Gel, and Cymetra [4, 6, 8]. The material is injected into the apex of the interarytenoid notch until fullness and blunting of the interarytenoid notch is seen [6]. Some advocate use of this technique is to determine which patients with mild clefts will benefit from surgical repair [10].

Open approaches are appropriate for type 3 or type 4 clefts, any cleft that cannot be accessed endoscopically, or any cleft that has failed endoscopic repair. These are performed through either a cervical or cervicothoracic approach. Three cervical approaches have been described: lateral approach with lateral pharyngotomy, lateral approach with posterior pharyngotomy, and anterior translaryngotracheal approach, which is the most commonly used.

The anterior laryngotracheal approach provides excellent exposure of the cleft, minimal neck dissection, and no risk to the recurrent laryngeal nerve. A horizontal neck incision is made, preferably in a skin crease, at the level of the cricothyroid membrane. Tissues are divided in the midline, the thyroid gland is identified and divided, and the anterior airway is exposed. A standard laryngofissure is performed, the length of which is determined by the length of the cleft. The cricoid and first two tracheal rings are divided in the midline. Midline can be confirmed endoscopically with simultaneous bronchoscopy. The thyroid cartilage is then divided, taking particular care to exact midline at the anterior commissure. Sutures may be placed at the anterior commissure to the thyroid cartilage to assure exact reapproximation.

Severe LTECs are life-threatening anomalies with high incidence of failed surgery due to the presence of respiratory and gastric secretions bathing the wound and due to directly opposing suture lines. Some sources advocate the use of vascularized tissue such as sternocleidomastoid flap [9] or tibial periosteum [7] as interposition between the esophageal and tracheal layers, whether at initial repair or for repair of a subsequent fistula. These patients can have refractory gastroesophageal reflux disease (GERD), which can be treated by gastric transection if necessary. Finally, they can also have significant tracheomalacia that may require a bifurcated tracheostomy tube [9].

Outcomes

The outcome of laryngotracheoesophageal cleft repair is highly dependent on the severity of the cleft. Grade 1 clefts can be present without the need for surgical intervention. The incidence of this is unknown. Grade 1 and some grade 2 clefts can be repaired endoscopically with good success. Grade 3 and 4 clefts require open repair, may require cardiac bypass or extracorporeal membrane oxygenation support, and have an associated mortality. The presence of congenital syndromes or comorbidities decreases the success rate for all types of LTECs.

Rahbar reported overall postoperative improvement following endoscopic repair in grade 1 and grade 2 clefts in children with no comorbidities of 80 % and 72 %, respectively. In children with comorbidities, outcomes were worse with improvement in 70 % and 60 %, respectively [14].

Cohen has published on injection laryngoplasty [6]. In a study of 16 patients with type 1 laryngeal clefts, the mean duration of symptom improvement was 3.3 months (Gelfoam 2.3 months, Radiesse Voice Gel 3.7 months). Five patients went on to have definitive surgical repair.

The largest published experience with severe LTECs is from Great Ormond Street Hospital [9]. Over a 10-year period, they treated nine patients with grade 3 or 4 clefts. The group included seven boys and two girls. The mean age at operative repair was 119 days. All nine survived the immediate postoperative period, and five were alive at time of publication at ages 9–21 years.

These patients had a significant number of comorbidities. The most common disorders were

gastrointestinal – all type 4 and one type 3 had microgastria; nine out of nine had documented severe GERD; two out of nine had Meckel's diverticulum; two out of nine had intestinal malrotation; two out of nine had enlarged left lobe of the liver. Other anomalies present in the patients with severe clefts included the following: two out of nine had cleft palate; one out of nine had left congenital diaphragmatic hernia and grade III pulmonary atresia; and one out of nine had left lower lobe pulmonary sequestration. Five of the nine patients had significant hearing loss [9].

Conclusion

Laryngotracheoesophageal clefts are an interesting embryologic anomaly with a wide variety of severity. Severe clefts present immediately at birth with severe respiratory compromise due to bronchial flooding with gastric secretions. These patients typically require tracheostomy, G-tube, and early surgical repair. The symptoms of less severe clefts can range from asymptomatic, to aspiration, to respiratory compromise. Type 1 laryngeal clefts require a high index of suspicion for diagnosis and is diagnosed by microlaryngoscopy and bronchoscopy. LTEC is often associated with comorbidities or syndromes, so workup and care should be coordinated.

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19 Postoperative Management of Routine Esophageal Atresia Cases

Christopher G. Turner and Russell W. Jennings

Introduction

Postoperative care is a critical component of complete surgical management. Compared to the relatively short preoperative preparation and the procedure itself, it is the longest stage in the sequence from diagnosis to therapy to return of health. Success of the operation and recovery of the patient depend heavily on the level and quality of the postoperative care. Operations on increasingly complex congenital diseases in both term and preterm infants have resulted from refinements in operative technique and, more importantly, advances in the surgical and anesthetic management of newborn infants and the coordination of this care in neonatal intensive care unit (NICU).

In reviewing the routine postoperative management of patients with esophageal atresia, recovery will be divided into three phases: (1) the immediate postoperative phase involving stabilization and recovery from anesthesia, (2) an early postoperative period involving the remainder of the hospitalization, and (3) a late phase after hospitalization. Care during the first two phases is directed at maintenance of homeostasis, treatment of pain, and the prevention and early detection of complications. Many principles of postoperative care in the esophageal atresia population are common to other areas of surgery. This chapter, therefore, will focus on operations on the esophagus and trachea including respiratory care, chest tube management, and the initiation of enteral nutrition. Complications will be reviewed in detail in other chapters but routine postoperative screening will be included here. It is important to note that many details of postoperative care in these patients are not standardized across institutions and a significant variation exists.

Immediate Postoperative Period

The major factors leading to early complications and death after esophageal atresia repair include prematurity, associated congenital heart disease, pulmonary complications, and anastomotic leaks with sepsis. The NICU has both the specially trained staff and equipment for early detection and treatment of these problems. The patient should be directly transported to the NICU and should be accompanied en route by a physician and other qualified attendants. The anesthesiology team generally has primary immediate responsibility for cardiopulmonary function, while the surgical team is responsible for the

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surgical wound and the other components not directly related to anesthesia. Transition of care to the intensive care unit is critical.

Postoperative Orders

Detailed treatment orders are required to direct postoperative care, and all members of the team must be aware of the important elements. The transfer of the patient from the operating room to the NICU is a tenuous period with the possibility for miscommunications as well as critical disturbances in the patient's condition. Patient care orders should describe for the nursing staff the diagnosis, the operation performed, and the patient's condition. All monitoring and therapeutic measures should be carefully detailed. Unusual or important orders should also be communicated to the nursing staff orally. Errors in postoperative orders, including medication errors and omission of important orders, are diminished by electronic order entry systems that contain postoperative order sets. Studies have shown that surgical checklists that involve team communication improve outcomes [1, 2].

Monitoring

The successful management of any critically ill infant requires the ability to measure and adjust appropriately the major physiological parameters. Infants are exquisitely sensitive to small changes in these parameters and, due to their size, possess the smallest reserve capacities of any group of patients in the hospital. As a result, invasive and noninvasive monitoring is an important element in management during the postoperative period. By necessity, the NICU has a host of technologies that should be used consistently and intelligently. Minimum requirements should include continuously recorded EKG, rectal temperature, blood pressure, respiratory rate, and hourly urine output. In those patients with compromised cardiorespiratory function, more invasive respiratory and hemodynamic monitoring may be necessary, including transcutaneous blood gas monitoring and interval blood gas measurements.

Temperature Management

Heat loss must balance with heat production in order to maintain a normal body temperature. Due to a large body surface to body weight ratio, the neonate is susceptible to heat loss and temperature imbalance. Mechanisms of heat loss include conduction from direct contact with cold surfaces, convection by the cooling effects of air currents on exposed skin, radiation to nearby objects such as the incubator wall, and evaporation of fluid from the skin and respiratory tract. As poikilotherms, preterm infants will not defend their body temperature and are particularly vulnerable. Cold injury can cause acidosis, hypoglycemia, increased oxygen consumption, and weight loss. In the postoperative period, the patient must be protected from heat loss. Conductive and convective heat loss can be reduced with the use of an incubator with an internal temperature of 32–36 °C, while radiation can be reduced with double-glazed incubators and evaporation can be reduced with humidification. Radiant warmer beds are less effective in protecting against heat loss but provide better access to the infant.

Neurologic Considerations

Newborns do experience pain after surgical procedures and should receive adequate analgesia [3, 4]. In the ventilated patient, options include morphine at a dose of 20–40 μg/kg/h by continuous intravenous infusion or fentanyl at a dose of 5–10 μg/kg/h.

Cardiac Considerations

Due to a relatively immature myocardium, newborns have a limited capacity to increase stroke volume, and their cardiac output is mainly rate dependant. When hypovolemia causes low

output, a reduction in elevated heart is the best guide to the adequacy of volume replacement, rather than blood pressure, which can be maintained at the expense of increasing heart rate and vasoconstriction.

The initial management to the infant with a low cardiac output indicated by tachycardia, vasoconstriction, oliguria, and hypotension is to increase preload by volume expansion with 10–20 ml/kg of plasma or albumin and then to reassess. Central venous pressure measurements may be useful in this context. Failure to raise output by increasing preload is an indication to attempt to decrease afterload or increase contractility by the use of vasoactive drugs.

Due to the common association with congenital cardiac anomalies, many of these patients will have complicated cardiac physiology requiring additional medical and surgical management.

Pulmonary Considerations

Unless there is a contraindication such as a congenital abnormality or injury to the nasal area, infants should be managed with nasotracheal tubes rather than oral tubes. Nasotracheal tubes are more comfortable and secure with attachment to the face and upper lip. The distal tip of the tube should reach only to the manubrium on the chest film in order to avoid entry into a main bronchus and single lung ventilation. The proximal end of the tube should be clear of the nose in order to avoid excoriation of the skin and erosion of cartilage, which can occur rapidly with pressure. The size of the tube should be adequate to avoid a significant leak under positive pressure but create a complete seal. Small tubes which leak at too low a pressure make positive pressure ventilation difficult, while large tubes with high leak pressure can cause airway pressure necrosis leading to subglottic stenosis, tracheal stenosis, and vocal cord granulomas, which may necessitate tracheostomy. Depending on the size of the child, 3–4 mm tubes may be used for newborns. Smaller tubes may be used for premature infants but are more susceptible to blockage from secretions.

Assiduous oral and pulmonary toilet is extremely important in the postoperative period in order to minimize the volume of swallowed saliva, maintain patency of the endotracheal tube, and prevent atelectasis. Infants should be kept in a semi-upright position. To avoid hypoxia and bradycardia, all patients should be inflated with 100 % oxygen by manual hyperventilation before suctioning. The catheter should not be large enough to occlude the lumen of the tube, which would create negative pressures and atelectasis. End-hole catheters are preferred to side-hole catheters that can injure the respiratory mucosa. Suction should be applied no longer than 10 s and only while the catheter is being withdrawn. Sterile technique with surgical gloves and a sterile catheter is important to avoid introduction of pathogens deep in the bronchial tree. Bradycardia is almost always caused by hypoxemia and should be an immediate indication to stop suction and begin manual ventilation. Precautions should be taken to protect the fresh esophageal anastomosis and fresh tracheal closure from the potential trauma of suction catheters. A sign posted at the bedside should display the distance to the esophageal anastomosis and the distance to the end of the endotracheal tube. Suction catheters should be directly measured and marked before use in order to avoid insertion to the depth of the esophageal anastomosis or the tracheal closure.

Humidification of the inspired air is a useful adjunct to pulmonary care. Too little humidification can cause dry secretions to block the endotracheal tube. Too much humidification, however, can cause condensation and the absorption of considerable amounts of water. The goal of optimal humidity is to provide fully saturated humidified gases (44 mg/L H_2O) at a temperature of 37 °C at the endotracheal tube. The temperature of the heated water bath type humidifier must be raised above the goal, to approximately 40 °C, to deliver the appropriate temperature at the endotracheal tube. Heated electric coils inside the inspiratory line can reduce heat loss as well as condensation.

The goal of ventilator management is to maintain normal gases with the lowest possible inspired oxygen and airway pressures. Generally,

infants with esophageal atresia have normal respiratory compliance and airway resistance. With a pressure-preset ventilator, set parameters include a PIP of 10–20 cm H_2O, a PEEP of 4–5 cm H_2O, a tidal volume of 6–8 mL/kg, a rate of 30–40 per minute, a FiO_2 of 0.25–0.35, and an inspiratory to expiratory ratio of 1:2 or 1:3. The adequacy of gas exchange must be confirmed with arterial blood gas samples. Adequate ventilation may compete with the infant's own efforts to breath. In the absence of pain, hypoxia, or acidosis, ventilation may be improved with muscle relaxants.

Chest tubes are used to manage fluid and liquid that accumulates in the chest, and may be used to monitor and control esophageal leaks.

Gastrointestinal Considerations

In the immediate postoperative period, the child should strictly have nothing by mouth. The stomach should be decompressed by continuous drainage of a nasogastric or gastrostomy tube. In the case of a nasogastric tube, the surgeon should place it in the operating room under direct vision to avoid the risk of injuring the fresh esophageal anastomosis. A nasogastric tube should never be passed blindly postoperatively.

Because of tension on the lower esophagus, infants after esophageal atresia repair are at increased risk of gastroesophageal reflux. The esophageal anastomosis will be more likely to stricture if irritated by acidic gastric contents. Patients, therefore, should be treated empirically with medications such as H1 acid blockade and possibly promotility agents.

Fluid Management

Restorative operations can cause significant disturbances in fluid and electrolyte status. Maintenance of normal balance is further complicated by the newborns immature renal system. Glomerular filtration rates are lower in the preterm compared to the term infant. Fluid balance depends on the balance between intake and fluid loss from the skin, urine, and stool. Full maintenance fluid requirements with dextrose/saline solution for the non-ventilated patient start at 60 ml/kg/day in the first day of life and increase to 100–150 ml/kg/day by 1 week of life. Due to humidification of the respiratory tract, it is common practice to give an infant on a respirator 70 % of the calculated maintenance requirement. Losses due to nasogastric suction should be replaced with normal saline. Normal electrolyte requirements are 2–3 mmol/kg/day of sodium and 3–4 mmol/kg/day of potassium. A urine output of more than 1 ml/kg/h is considered adequate following surgical procedures in the newborn.

Antibiotics

Broad-spectrum antibiotics should be continued during the perioperative period. Antibiotics should be adequate to cover both oral and skin flora as both are exposed to the wound during surgery.

Early Postoperative Period

After the initial stabilization and avoidance of acute critical care complications, the focus turns to complete recovery and independence from the many medical supports of the intensive care unit. In the esophageal atresia patient, this requires extubation, removal of all drains, and commencement of oral feeds. During this period of time, there are specific complications to monitor and prevent, specifically esophageal anastomotic leaks, esophageal strictures, and recurrent tracheoesophageal fistulas.

Ventilator Management

The use of long-term paralysis and mechanical ventilation while maintaining neck flexion has been advocated by some to minimize the risk for anastomotic disruption when there is severe tension [5–8]. The rationale is to prevent disruptive force at the anastomotic site by flexion of the

neck and paralysis of the striated muscles in the proximal part of the esophagus [6, 9]. However, in our experience, the ventilator should be weaned as quickly as possible to minimize trauma from positive ventilator pressure or direct contact with the endotracheal tube. Caution should be taken with the actual extubation. Replacement of the endotracheal tube may damage or rupture the trachea at the site of the fistula closure. Ideally, the infant should be able to breathe spontaneously on the ventilator. Furthermore, the need for narcotics to control pain should be low to avoid depressed respiratory drive and apnea. In the unavoidable event of reintubation, an experienced operator should place the tip of the endotracheal tube just beyond the vocal cords. Passage down the esophagus could result in anastomotic disruption, while passage too far into the trachea could result in tracheal laceration.

Drain Management

The drain in the chest should be maintained until a barium swallow demonstrates the integrity of the esophageal anastomosis. A fistula may be identified directly on the barium swallow or may be inferred from the appearance of saliva in the chest tube. Alternately, an extrapleural effusion on chest radiographs may be associated with anastomotic leakage. In order to protect the anastomosis, the chest tube should remain if a significant fistula appears. The vast majority of esophageal leaks controlled by chest tube drainage should spontaneously seal with time.

Diet Advance

In some centers, feeds are started a day or two after the surgery in patients with a gastrostomy tube. Alternately, feeds are started through a nasogastric feeding tube that was placed at the time of the operation. During feedings, all patients should be flat with the head of the bed elevated and monitored closely because of the high prevalence of gastroesophageal reflux. Oral feedings are then initiated only after a normal barium swallow conducted 5–7 days after the operation.

In our center, nutrition is provided parenterally for the first 7–10 days. Feeds via nasogastric tube are initiated on postoperative day 1 at 1 cc/h and increased as tolerated. If there are no signs of a leak clinically during the first 7–10 days, the child is fed orally. A postoperative esophagram to rule out leaks or gastroesophageal reflux is obtained prior to the first oral feeding only if indicated. Feedings are advanced as tolerated and the patient is discharged home when they are at goal.

Because the suck reflex is not adequate until 34–36 weeks gestation, the nasogastric tube should be removed only after oral feedings are established for infants younger than 36 weeks gestation. The presence of a transesophageal feeding tube exacerbates the reflux of gastric contents and justifies keeping the patient in an intensive care unit.

Management of Associated Anomalies

A second anomaly occurs in nearly half of babies with tracheoesophageal anomalies. Many organ systems may be involved: most notably the complex of vertebral, anorectal, tracheoesophageal, radial limb, and renal. It is beyond the scope of this chapter to review the diagnosis and management of these complicating congenital defects. It is, however, important to note that they may occupy much of the management time and effort in the early postoperative period.

Anastomotic Leaks

There are several specific signs of an anastomotic leak such as saliva in the chest tube and gas bubbles in the mediastinum. There are also several nonspecific signs such as fever, elevated white blood cell count, pneumothorax, and shock. There is a general correlation between the time of onset of the leak and its seriousness. Earlier

leaks, occurring in the first 3 days, are more significant. Most of these can be treated nonoperatively, but some surgeons may resort to a cervical esophagostomy. Later leaks, occurring between 3 and 10 days from the operation, are less significant and can usually be treated by chest tube drainage, antibiotics, and hyperalimentation. Later in the hospital course, it is important to note that leaks make an anastomotic stricture more likely, probably as a result of the local inflammation and scarring.

Esophageal Strictures

Anastomotic strictures are the most common postoperative problem in most series. Anastomosis of a large upper esophageal pouch to a tapered thin-walled lower esophageal segment under tension predisposes to stricture formation. Swallowing by the infant may dilate the narrow anastomotic site and diminish the size discrepancy. Some surgeons prefer prophylactic dilations in the postoperative period, while others dilate only when needed. Overall, 20–35 % of patients require several dilations regardless of whether one or two prophylactic dilations were done. In some programs, the infant returns at 6 weeks and 3 month after the operation for dilation with rubber dilators in the clinic. Additional dilations are performed as needed, and if more than three are required, the infants may be considered to have a recalcitrant stricture. In the absence of reflux, these dilations are usually successful. However, when reflux is present, fundoplication may restore their efficacy [10, 11].

Recurrent or Unsuspected Congenital Tracheoesophageal Fistulae

In the early postoperative period, tracheoesophageal fistulae may be identified either because they have recently developed or they were not previously diagnosed. Symptoms that suggest a tracheoesophageal fistula are the same as those in the preoperative period, and include wheezing, coughing, choking, cyanosis, apnea, and recurrent pneumonias. These symptoms overlap with other possible complication of stricture, gastroesophageal reflux disease, and tracheomalacia. As a result, suspicion should be high, and a child with a history of repaired esophageal atresia and these nonspecific symptoms should have a complete evaluation to rule out a tracheoesophageal fistula [12].

A missed congenital upper-pouch tracheoesophageal fistula will be revealed with the initiation of postoperative feeds and be associated with coughing, choking, and signs of aspiration without signs of mediastinal infection and inflammation. A recurrent fistula, on the other hand, may appear years after the operation, when perhaps a small chronic abscess develops from a leak or erosion of sutures between the esophageal and tracheal repairs. The severity of the inflammatory process determines the presence of fever, elevated white blood cell count, and/or mediastinal air.

Evaluation should include a contrast study and endoscopy to discover a recurrent fistula at the anastomotic level or a missed congenital fistula at a higher level. If a fistula is identified, surgical repair is warranted. No delay is necessary unless there are additional medical problems that need to be stabilized. After separation and ligation of the tracheoesophageal fistula, a flap of tissue can be inserted between the trachea and the esophagus to reduce the chance of recurrence. An approach through the old incision allows for only one scar, provides direct access to the problem, and does not introduce the potential for infection into the other side of the chest. An approach through the neck is often preferable for missed congenital upper-pouch tracheoesophageal fistula.

Late Postoperative Period

After discharge from the hospital, the major complications that need to be monitored involve the esophagus and the trachea. Here we will review gastroesophageal reflux, tracheomalacia, and associated lower esophageal stenosis.

Gastroesophageal Reflux

Gastroesophageal reflux disease (GERD) commonly occurs in the postoperative esophageal atresia patient as a result of the combination of lower esophageal dysmotility, tension on the gastroesophageal junction, and chalasia of newborns. GERD is problematic because it stimulates anastomotic stricture formation and esophagitis, as well as producing pulmonary problems and apneic episodes with aspiration of gastric contents [13–16]. Evaluation is appropriate either with repair of a long gap (>2 cm) due to greater tension on the gastroesophageal junction, when signs of a stricture appear, or when a stricture recurs promptly after dilation. A contrast study should be the primary evaluation, but, if negative, pH monitoring and radio-labeled technetium swallow studies may be indicated.

Infants with GERD are initially treated medically with prone positioning, elevated head of bed, and thickening of feeds [17]. The reflux should improve with the passage of time [18]. If medical treatment does fail, a Nissen fundoplication or other anti-reflux procedures should be considered. However, results are not uniformly beneficial because the reflux can recur and the dysphagia, which is intrinsic to the atresia repair, can be aggravated [19, 20]. Persistence of Barrett's esophagus after anti-reflux surgery suggests that this particular problem should be addressed early and followed closely for life [21].

Tracheomalacia

Some degree of tracheomalacia is usually present in patients with esophageal atresia and is more common when a tracheoesophageal fistula is also present [22–24]. Mild forms cause occasional noisy breathing with the characteristic barky cough (TOF cough), while more severe forms can cause life-threatening apneic and bradycardic spells. More severe grades may also prevent the infant from being weaned from the ventilator or may lead to recurrent pneumonia [25].

Diagnostic studies include lateral airway fluoroscopy, cine CT of the airways, and dynamic bronchoscopy. The presence of the innominate artery will produce characteristic anteroposterior narrowing just above the carina. The spectrum of tracheal involvement may include a localized region or be more generalized. With severe forms, the anterior and posterior tracheal walls will collapse and occlude the airway during expiration or coughing [26].

As with GERD, symptoms generally improve over time. However, with severe apnea or failure to wean the ventilator, surgical therapy may be necessary. The initial operative approach is typically an aortopexy with elevation of the ascending aorta artery, which will place tension on the trachea and reduce the risk of collapse. In severe cases, this can be a critical therapeutic maneuver [25, 27–29].

Associated Lower Esophageal Stenosis

Lower esophageal stenosis is a rare association that may not be discovered until 6–12 months of age because the symptoms are attributed to common feeding problems, anastomotic problems, or lower esophageal dysmotility. If the condition is suspected at the time of repair on account of an unusually large lower esophageal segment, a contrast study should be performed when appropriate. Obstruction in the distal portion of a dyskinetic esophagus increases proximal esophageal dilation and results in further dysfunction. If the obstruction tapers and results from fibromuscular hyperplasia, conventional dilation should be adequate. If the obstruction is discrete and results from tracheobronchial remnants or a fibromuscular shelf, resection with reanastomosis should be performed to prevent further increases in esophageal expansion and dysfunction.

Conclusion

Postoperative management is critical in the successful recovery of patients with esophageal atresia. This care includes the immediate acute care through to the chronic complications later in life.

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Part V

Repair of Long-Gap EA: The Difficult End of the Spectrum

The Long-Gap Esophageal Atresia Problem

20

John E. Foker

Introduction

The repair of the most common form of esophageal atresia (EA) with a tracheoesophageal fistula (TEF) from the lower esophageal segment to the trachea is often a pediatric surgeon's favorite operation. Beginning with a fatal lesion if untreated, the repair requires skill and judgment, and, as an added bonus, the long-term outlook may be essentially normal. For the majority of EA/TEF infants, the operative result is entirely satisfactory and pleases both the families and the surgeon.

The EA spectrum, however, is broad in terms of the severity of the lesions and leads to treatment approaches which are equally wide. For the surgeon, the difficulty with the repair arises in rough proportion to the length of the gap between the esophageal ends. As the gap increases, the likelihood of a prompt and satisfactory primary esophageal repair decreases and often puts the patient on a complicated and difficult road.

A long gap may also be acquired. When an initial repair of an EA/TEF defect has failed, a considerable space may be left between the esophageal segments, particularly if the upper pouch is converted to a cervical ("spit") fistula. These patients now have the residual difficulties of an unsatisfactory initial operation added to the considerable distance between the esophageal ends.

It has long been recognized, however, that an esophagus-only repair is best [1, 2]. This realization has been the driving force to achieve a primary repair despite the problems long gaps pose for surgeons. The value of a true primary repair lies in its much closer approximation of normal with the likelihood of improved short-term and longer-term results. The important consequence of a long gap between segments, either initially or secondarily, however, is that a true primary repair becomes very difficult or, often, impossible. As a result of the problems and treatment difficulties created, long gap (LG) EA has received a great deal of attention.

Definition

The definition of a long gap is not settled, although it has been proposed that it begins at a preoperative gap over 2 cm [3–5]. The definition will remain elusive, however, because it is subjective in nature. When planning an EA repair, what will be considered to be a long gap is

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affected by many factors not easily quantified. The patient's size and condition, the anatomical variations present, the perceived tissue quality, and, very importantly, the experience of the surgeon will affect the judgment. All of these will weigh on any surgical decision; consequently, it does not seem helpful to try and define "long" any more precisely than a gap which may prevent a primary esophageal repair. Any definition, moreover, will only be the roughest of guides because in the operating room, the gap length will be in the eye of the beholder [6].

Even though what constitutes a long gap remains unsettled, the term ultra-long gap has also been used. An ultra-long gap has been proposed to be at least 3.5 cm long, at least in part to define a gap that is beyond a primary repair, a length generally considered too long for a true primary repair [7, 8].

What gap length may prevent a primary repair has also changed with the increasing realization that some degree of tension may not preclude a satisfactory anastomosis. Although what is considered a repairable gap length may have increased, experience still suggests that repairs are not completely reliable much beyond 3.0 cm. Certainly, whatever length might be considered repairable, it would not extend to the far end of the 3.5–6 cm range for which it has been claimed that pediatric surgeons "would almost always perform a primary anastomosis…" [9]. And even only "in some cases" would "gaps greater than 6 cm…not be amendable to primary repair" [9]. These statements are very misleading because that author still considered it a primary repair if the stomach was pulled part way up into the chest so the esophageal segments could be joined together (Coran AG (1996), Personal communication).

We believe, however, that a true primary repair, defined as an esophageal repair without myotomies and with the stomach left below the diaphragm where it belongs, should be the goal [10]. These requirements will provide the configuration to allow an outwardly normal long-term outcome to be realized. The partially intrathoracic stomach, however, is quite unsatisfactory for both the short and long term, principally because of obligatory gastroesophageal reflux (GER) and its predictable consequences. A true primary repair, in contrast, may have GER and/or strictures, but these can be treated and not compromise the long-term results.

The Formation of Long-Gap EA

What determines the gap length when EA occurs is not well understood, although there are biomechanical factors that logically help explain it. The most important factor affecting the gap length is whether or not the original maldevelopment results in the lower esophageal segment being attached to the airway. This is the most common form of EA (type C), and it typically has a shorter gap because the lower segment will necessarily lengthen as the fetus grows (Fig. 20.1). As a result, the common form of EA with a lower TEF is usually amendable to initial primary repair. Occasionally, however, there are structural differences in EA/TEF which may affect the surgeon's impression about the ease of repair. If the lower esophageal segment enters the right or left main stem bronchus or even straight into the carina rather than up along the back of the trachea, the gap may seem too long [11]. A fistula from the upper segment to the trachea (type B) has the opposite effect of a lower TEF, because it decompresses the upper pouch reducing the growth signal, so it is smaller, and higher, and the gap is longer (Fig. 20.1). These variations in anatomy may affect the judgment about the gap length and the suitability for a true primary repair. The surgeon, of course, should be circumspect about true primary repairs when the anatomy is not entirely suitable.

In "pure" EA without a lower TEF (type A), a gap is usually present between the upper and lower esophageal segments rather than the atretic segment being a solid cord (Fig. 20.1). When the lower segment is not attached to the airway, its growth in the fetus is quite variable and the eventual gap may be very long. Occasionally, a cord is present from the end of the lower segment to the airway or up into the posterior mediastinum which usually to encourages growth of the lower

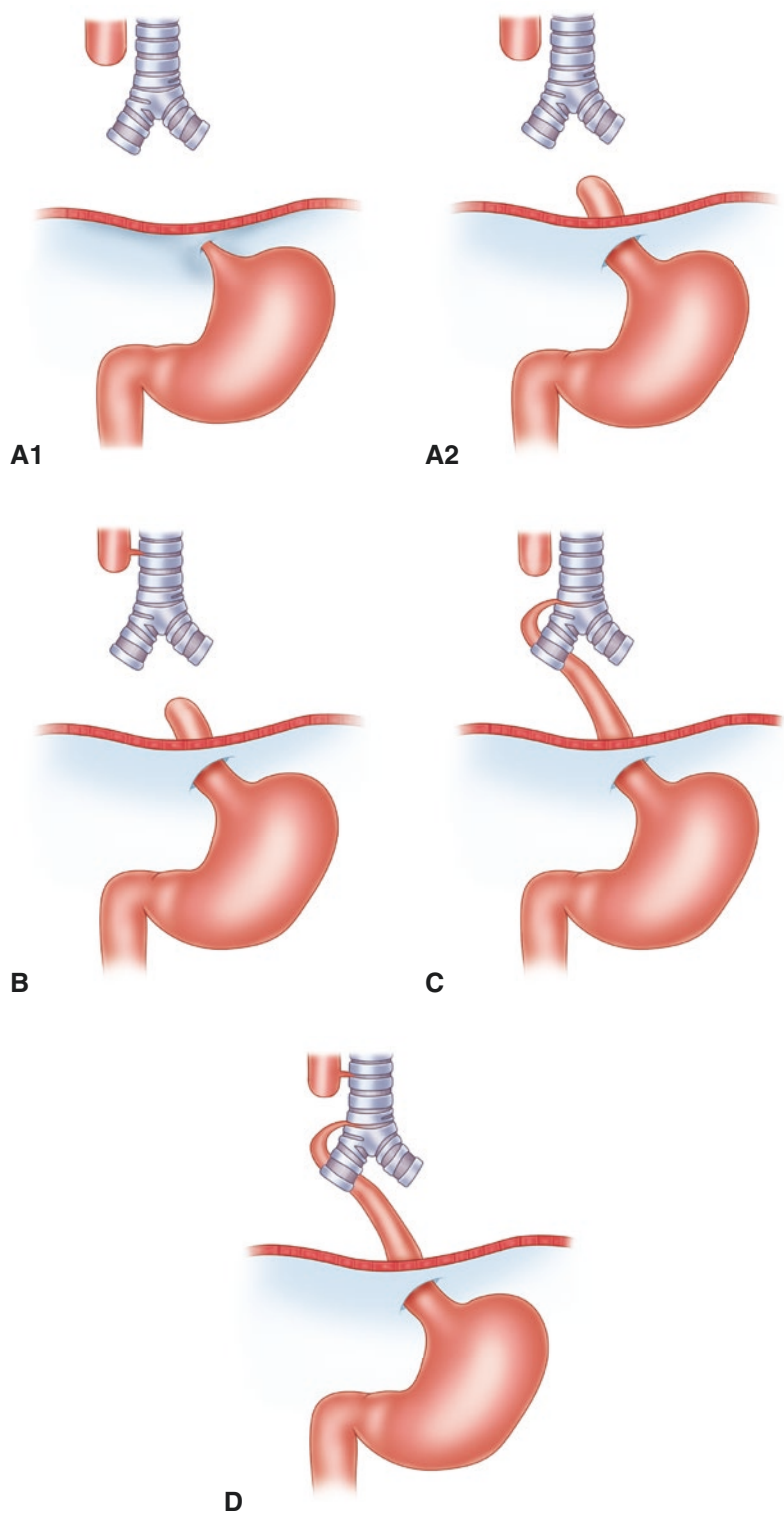

Fig. 20.1 The pathological spectrum of esophageal atresia (EA). Panels (**A**–**D**) illustrate the major subdivisions within the virtually continuous EA spectrum. Depicted are the upper and lower esophageal segments, diaphragm, stomach (not to scale), and proximal tracheobronchial tree. For repair of EA, the major consideration is the length of the gap between the upper and lower segments. Considerable variation exists within the types, as depicted in type A, where the lower segment may not be discernable (A_1) or may reach above the diaphragm (A_2). Decompression through a fistula into the trachea seems to result in a smaller upper pouch and may increase the gap in type B. The most common form (~75%) has a tracheal fistula from the lower segment, and this connection results in adequate length and a shorter gap (type C). A tracheal fistula from both segments adds complexity, but the gaps are not long (type D). A fistula-only form has no atretic segment and is not shown

esophagus. Even when there is not a cord, the lower end may be relatively long and reach well above the diaphragm (type A_3); however, in other cases, only a tiny 3–4 mm-long primordium may be present and located well below the diaphragm, leaving a very long gap (type A_1) (Fig. 20.1). Why these differences in gap length occur is not always clear but presumably is related to greater or lesser biomechanical forces which stimulate growth of the lower segment [12].

The prime mover in the growing of the esophagus is the spinal column with its growth plates which provide the tension through the varying attachments to the esophageal segments. Tension is translated into intracellular signals producing growth. A large body of basic studies have provided an understanding of the many molecular mechanisms involved in cell growth stimulated by these biomechanical factors [12]. The importance of axial tension in producing esophageal growth was confirmed by inducing growth with traction sutures to solve the long-gap problem [10, 13].

There are also several associations found in LG-EA which may contribute to the gap length. EA associated with an aortic arch anomaly including an aberrant origin of the subclavian artery, either right or left, often has a long gap [14]. The aberrant arteries course between the upper and lower segments and seem to provide a reason, if not a mechanism, for the longer gap. A preoperative cardiac evaluation, including echocardiography, in EA newborns, should reveal the presence of an aberrant subclavian artery and alert the surgeon to the possibility of a long gap.

Other developmental anomalies have been found in apparent association with a longer gap. An absence of the azygos vein with LG-EA has been described, but the relationship is more difficult to understand [15]. Because the presence of this anomaly would not be determined preoperatively, the value of this finding is limited. These authors also disputed the value of 13 ribs in predicting a LG-EA which had been previously proposed [15, 16]. These and other associations are presumably the result of alterations in the usually carefully orchestrated biomechanical forces in the area.

Preoperative Evaluation of Gap Length

Given the variability of the EA spectrum and consequently of gap length, a preoperative evaluation is very valuable. The question of gap length quickly arises for babies with a blind upper pouch and a gasless abdomen which suggests a pure atresia (type A) or a presumed blind lower segment with an upper pouch TEF (type B). With a presumed blind lower pouch, a gastrostomy tube (G-tube) is usually placed to allow feeding and to enable the distance between the blind segments to be determined. Although the measurement of gap length will raise questions about its reliability and its significance, it will help in preoperative planning and is what will be needed to achieve a true primary esophageal repair.

There are two commonly used methods of measurement, each with advantages and disadvantages. Any gapogram, moreover, is a two-dimensional representation of what is a three-dimensional problem, and the real distance may be longer.

The method we favor is the injection of contrast material into the G-tube to outline the lower esophageal segment and a radiopaque catheter or other contrast agent to determine the length of the upper pouch. Evaluating the two segments together will provide an unstressed "gapogram" and an estimate of a gap length. A disadvantage of the unstressed measurement is that it does not estimate the gap length after dissection nor the effect of moderate traction pulling the ends together. Nevertheless, this estimate of nonstressed gap length will provide adequate information to formulate an operative approach. The lower segment is usually the determining factor in the long gap and whether it resembles A_1, A_2, or A_3 will help understand what lies ahead (Fig. 20.1)

The other measurement method places an instrument such as an endoscope or a Hegar dilator into the upper and lower segments in order to push them together. Many pediatric surgeons use this method, but it has several drawbacks. First, the configuration of the lumen will not be defined at either end. More importantly, pushing against

newborn tissues with dilators may cause the gap to largely disappear and give the false conclusion that a relatively short gap exists. We have even seen examples where the dilators pushed the stomach and diaphragm well up into the chest and appeared to almost close the gap when virtually no lower segment was present. This considerable distortion may make the reality of what one finds in the operating room very daunting and cause the predicted primary repair to be quickly abandoned.

Because the commonly used methods to determine gap length preoperatively have drawbacks, the surgical approach must be flexible [13]. In the operating room after dissection and a trial of pulling the ends together, the last centimeter or two of gap may be very difficult to close. At this point, the decision should be made. Once open, the esophageal ends must be put together; otherwise, it will be necessary to create a spit fistula and close over the lower segment, maneuvers which may end the hope of a primary repair (see Chap. 25: Esophageal Growth Induction and a Flexible Approach to Long-Gap Esophageal Atresia Repair, Foker).

Traditional Long-Gap Treatment Methods

The wide spectrum of LGs exists largely because of the variability in the size of the lower segment which may reach the level of the carina or only be a primordial nubbin (Fig. 20.1). For the more favorable end of the LG spectrum, the lure of a primary repair has long been present. In an early report, however, an initial primary repair of LG-EA patients produced very unsatisfactory results ranging from a major, persistent leak to disruption of the anastomosis [17]. At the time, these bad results were considered predictable, and it was widely advocated that an anastomosis should be essentially tension free or another treatment method be chosen. Although there is evidence that a well-constructed anastomosis will withstand tension, it seems much wiser to select an intermediate approach that will relatively quickly produce sufficient growth for a more straightforward true primary repair [7, 10, 13] (see also: Chap. 19: Delayed Primary Anastomosis in the Management of LG-EA; Chap. 25: The Flexible Approach for Primary Repair of Long Gaps).

The spectrum of LG-EA has led to a variety of methods to treat these patients and these fall into one of three approaches. A more complete presentation of the methods will be found in the succeeding chapters in this section on Repair of Long-Gap EA.

For a mild to moderately long gap (about 3–5 cm), a period of waiting, with or without bougienage, has been used with the hope that growth stimulated by some combination of swallowing, gravity, G-tube feeds, intermittent pressure by bougienage, or even the force of electromagnets may close the gap sufficiently to make a primary repair possible [18–22]. Although in our experience catch-up growth does not occur, nevertheless for some patients, this has been a satisfactory approach and is explained more fully in the chapter titled, Delayed Primary Anastomosis in the Management of Long-Gap Esophageal Atresia.

For moderate gaps, surgeons have attempted to increase the length of the segments by such methods as upper segment myotomies or flaps to lengthen the upper pouch and allow a primary repair [22–26]. Some have even placed a suture through the segments to develop a fistulous tract between them which can later be dilated [27]. These methods may have predictable potential problems such as significant strictures or a diverticulum from an unsupported esophageal wall after a myotomy. A diverticulum will interfere with transit down the esophagus and, on occasion, has become quite large and even life-threatening [28, 29].

The creation of a flap to lengthen the upper pouch may be useful, although it will produce an ornate suture line. There is limited reported experience with the flap techniques, but if the wall remains full-thickness and the resulting stricture manageable, the result should be satisfactory [25, 26].

An intermediate approach consists of either widening the opening to allow the gastroesophageal (GE) junction to be brought up through the

esophageal hiatus or lengthening the stomach to facilitate the partial pull-up [9, 31] (Coran AG. Personal communication, 1996.). Patients with an intrathoracic GE junction, however, have obligatory reflux which may lead to very unsatisfactory consequences. Effective treatment will require the GE junction to be brought back below the diaphragm, and, depending on the amount of stomach above the diaphragm, it may not be easily accomplished. The alternative method of using a Collis gastroplasty, ostensibly to lengthen the esophagus, leaves a tube of stomach and the real GE junction within the chest which does not seem to be a satisfactory choice for a child hoping to realize 70 good years.

It has been stated that unless the lower segment ends above the diaphragm, a "primary repair" of any type is not possible [31]. Although we disagree with this conclusion, in most cases, it will lead the surgeon to a staged repair – the third general approach to LG-EA. Whether from the original gapogram or by surgical exploration, if a primary repair is judged not possible initially or in the near future, an initial cervical fistula and a G-tube will usually be placed. These allow the patient to grow until a later interposition graft can be used to establish continuity. A staged approach may also be used after a failure of the initial EA/TEF primary repair when the upper esophagus is converted into a spit fistula and the lower esophagus oversewn. For these LG-EA patients, a primary esophageal repair no longer seems possible, and the future typically holds an interposition graft, almost always either the stomach or colon [32–34]. Moving either of these organs into the chest, however, may lead to adverse consequences resulting in a state of chronic disease.

The Flexible Approach to LG-EA

Given the uncertainties and problems described with longer gaps, the surgeon should have a flexible approach for any defect beyond the routine EA/TEF repair. Traditionally, as noted, there has been wide variation in the repairs used to solve the long-gap problem. The variation in the operations indicates both the width of the EA spectrum and the elusiveness of satisfactory outcomes. What has changed more recently is the ability to reliably and rather rapidly induce growth in the atretic segments, making possible the desirable goal of a true primary esophageal repair across the EA spectrum [10]. The ability to induce growth has been so effective it has closed gap lengths of up to 16.5 cm and produced an outwardly normal esophagus beginning with lower segments only 3–4 mm long and located far below the diaphragm. Several techniques to provide axial tension and induce growth have been devised to meet the different configurations of the esophageal segments. The spectrum of operative approaches is described more fully in the chapter titled, Growth Induction and The Flexible Approach for Primary Repair of Long-Gap EA.

The long-term consequences of the surgical approaches to LG-EA should be considered because, to achieve the goal of 70 good years, the treatments must not set in motion significant new problems. The several current approaches to LG-EA also raise the conflict of a relatively easy solution, e.g., a spit fistula and G-tube and later interposition, with one that may take more time initially such as a growth procedure. The staged approach can be performed, usually at relatively low risk and with reasonable length of stay; however, they bring short- and long-term problems of their own, creating new types of chronic disease.

Because the spectrum of EA is so broad, it is important that the surgeon treating the severe forms be well acquainted with the lesions and the various repairs needed to achieve a satisfactory end result. Repairs using growth induction have the capability to achieve a true primary repair with virtually any initial LG-EA lesion; however, worldwide experience has shown the procedures become increasingly more difficult toward the severe end of the spectrum. It would seem logical, therefore, that a very difficult initial EA lesion be referred to a place of greater experience, so the infant will ultimately enjoy the benefits of a true primary esophageal repair, and this plea has been made [35].

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Delayed Primary Anastomosis in the Management of Long-Gap Esophageal Atresia

21

Prem Puri and Florian Friedmacher

Introduction

Esophageal atresia is a complex congenital malformation of unknown etiology with a frequency of 1 in 3,500 live births [1, 2]. Pure esophageal atresia without tracheoesophageal fistula is an uncommon anomaly, comprising 8 % of all patients with esophageal atresia, with an expected incidence of 1 in 40,000 live births [3]. Despite improvements in prenatal diagnosis [4, 5], esophageal atresia is still life-threatening, and without any surgery, it is fatal. The first survivors of a staged repair with a primary gastrostomy and a delayed esophageal reconstruction were reported by William Ladd in 1939 [6]. Cameron Haight was the first to perform a successful primary repair of esophageal atresia in 1941 [7]. From then on, advances in surgery, pediatric anesthesia, neonatal intensive care, and parenteral nutrition have increased the survival rate following reconstruction from universally fatal to approximately 95 % [8]. Today, even newborns with very low birth weight and severe cardiac malformations survive [9]. Nevertheless, the high incidence of prematurity, additional anomalies, and long-gap esophageal atresia complicate the care of these patients [10, 11] and may preclude an immediate primary repair. Thus, surgical management of patients with long-gap esophageal atresia represents a major challenge to most pediatric surgeons [12, 13], especially when a primary end-to-end anastomosis is not possible. The distance between the upper and lower esophageal segment and the presence of a tracheoesophageal fistula will determine the operative management. There is a consensus among most pediatric surgeons that every effort should be made to conserve the native esophagus, as no other conduit can replace its function in transporting food from the oral cavity to the stomach [14]. Over the last 70 years, there have been considerable changes in the operative treatment of long-gap esophageal atresia, and it is widely accepted that a delayed primary anastomosis of the esophagus is not only achievable but also the preferred option in the majority of such cases.

History

Over the last four decades, various techniques have been described to reduce the distance between the two esophageal ends to achieve a delayed primary anastomosis. In 1965, Howard and Meyers [15] were the first to advocate periodic manual bougienage of the upper esophageal segment, producing elongation of the pouch,

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followed by a subsequent primary anastomosis 5–8 weeks later. Bougienage of the distal esophageal pouch in addition to the proximal pouch was reported first by Lafer and Boley [16] in 1966. Rehbein and Schweder [17] used a temporary silver prosthesis to create a fistula between the two esophageal segments. In 1972, Thomasson [18] described an elongation of the upper esophageal pouch by mercury-filled bags, and Livaditis et al. [19] introduced circular myotomy of the esophagus to enable a primary anastomosis. The use of silk sutures for esophageal auto-anastomosis by producing a mucosa-lined fistula was demonstrated first by Shafer and David [20] in 1974. Hendren and Hale [21] reported their experience with electromagnetic stretching of the two esophageal segments in 1976.

In 1981, Puri et al. [22] published their observations in newborns with pure esophageal atresia that spontaneous growth and hypertrophy of the two esophageal segments occur at a rate faster than overall somatic growth in the absence of any form of mechanical stretching. The maximal natural growth of the esophageal segments occurs in the first 8–12 weeks of life [22]. The stimuli to such natural growth are the swallowing reflex and the reflux of gastric contents into the lower esophageal pouch [23]. Therefore, Puri et al. [22, 23] recommended initial gastrostomy and continuous suction of the upper esophageal pouch followed by delayed primary anastomosis as an ideal procedure for the management of newborns with long-gap esophageal atresia. In 1994, Boyle et al. [24] confirmed that even in cases of ultralong-gap (>3.5 cm) esophageal atresia, a delayed primary anastomosis is achievable. Foker et al. [25] showed in 1997 that esophageal growth is rapid if continuous traction sutures are applied in the esophageal segments, producing significant lengthening within days.

Initial Preoperative Management

Once the diagnosis of esophageal atresia is established, the next step is to perform a preliminary feeding gastrostomy to provide adequate nutritional support (Fig. 21.1). Furthermore, a 10-F Replogle sump-suction catheter should be placed into the upper esophageal pouch and is kept under continuous suction to prevent aspiration pneumonia. The patient is maintained in a head-down position (as far as possible) for efficient suction of the upper esophageal pouch and to allow reflux of gastric juice contents into the lower esophageal segment. The gastrostomy is kept plugged between feedings to encourage gastroesophageal reflux and distension of the lower esophageal pouch. An important factor responsible for hypertrophy of the lower esophageal pouch is the reflux of gastric contents owing to the incompetent gastroesophageal junction of young infants.

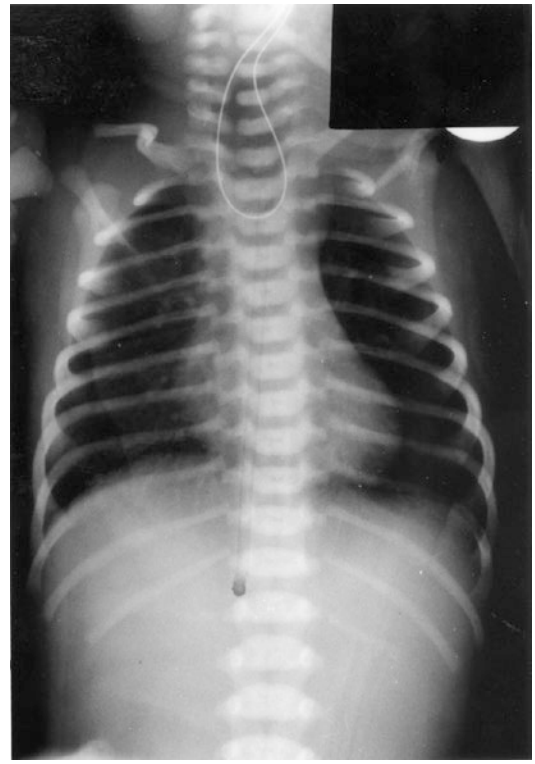

Fig. 21.1 Chest radiograph of a newborn with long-gap esophageal atresia

A variety of techniques for monitoring the elongation of the esophageal pouches have been described. Injection of water-soluble contrast via the gastrostomy tube may be the simplest and oldest technique performed to evaluate the lower esophageal pouch. Most authors favor radiological

assessment of the intervening gap by insertion of a rigid metal dilator in both the upper and lower esophageal pouches [26, 27]. The distance between the two ends can be quantified either by placing the patient on a ruler with radiopaque markings or by counting the number of vertebral bodies between the two segments (one vertebral body is equal to roughly 1 cm). It is important not to apply excessive force to the dilator while measuring the gap between the segments because it can produce errors in estimation of the distance between the two segments [28]. Caffarena et al. [29] first described placing an endoscope in both the upper and lower esophageal pouches for measurement of long-gap esophageal atresia. Chan and Saing [30] combined flexible endoscopy and fluoroscopy in the assessment of the gap between the two esophageal pouches. Gross et al. [31] demonstrated how fiberoptic endoscopy enables measurement of the gap in esophageal atresia. Other investigators used computer tomography scanning for evaluation of neonates with esophageal atresia [32, 33]. Measurement of the gap between the esophageal segments is initially made approximately 2 weeks after gastrostomy and is repeated at 3-week intervals (Fig. 21.2).

Although some centers have allowed these patients to return home for a few weeks on nasopharyngeal suction and gastrostomy feedings [3, 34], generally the patients are kept in the hospital until primary esophageal anastomosis is performed [22, 23, 35, 36].

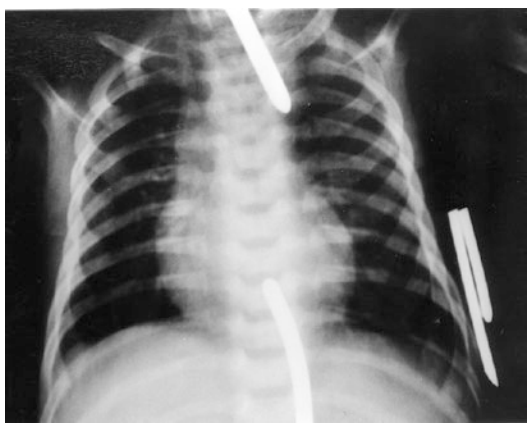

Fig. 21.2 First measurement of the gap between the upper and lower esophageal segment by using radiopaque bougies at 3 weeks of age. The gap is approximately five vertebral bodies long. Care must be taken to not exert excessive pressure on the bougies

Delayed Primary Anastomosis

Puri et al. [22] have shown that the maximal spontaneous growth of the two esophageal segments occurs in most patients by 8–12 weeks of age, and this correlates with doubling of birth weight. By this age, the gap between the two esophageal pouches usually is less than 2 cm (Fig. 21.3) [23, 36, 37]. Therefore, it is recommended to perform delayed primary anastomosis when the patient is 3–4 months old. Successful primary anastomosis with delays of up to 12 months [34] and initial gaps of up to 7 cm [38] or eight vertebral bodies [39] has been reported.

The surgical approach for delayed primary anastomosis of the esophagus in long-gap esophageal atresia is similar to that of repair of esophageal atresia with tracheoesophageal fistula. Lobe et al. [40] also have described thoracoscopic repair of esophageal atresia. A standard right posterolateral thoracotomy is performed via the fourth intercostal space using the extrapleural approach. The advantage of the extrapleural approach is that a postoperative anastomotic leak does not contaminate the pleural cavity, allowing prolonged chest-tube drainage. At the time of the operation, the esophageal pouches appear thickened and hypertrophied [28]. Dissection and mobilization of the upper esophageal pouch usually will facilitate approximating the esophageal segments with minimal tension. Several investigators have reported using circular myotomy to obtain additional length for the upper pouch [22, 34–36, 38, 41–46]. Postoperatively, the patient is nursed in the neonatal intensive care unit. The chest drain is left on water seal, intravenous fluids are administered, and antibiotic prophylaxis is continued. If the esophageal anastomosis has been performed under significant tension, the patient is electively paralyzed and mechanically ventilated for five postoperative days. At 7–10 days post surgery, a water-soluble contrast study should be carried out (Fig. 21.4). If no leak

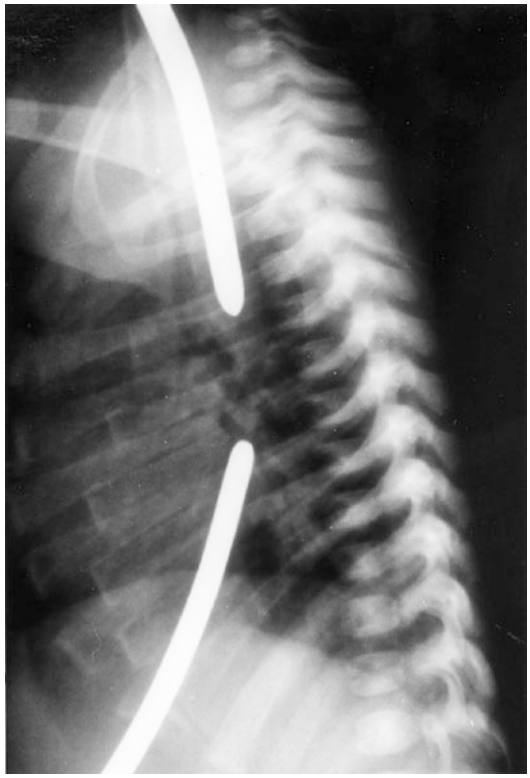

Fig. 21.3 Significant reduced esophageal gap in the same patient at 14 weeks of age

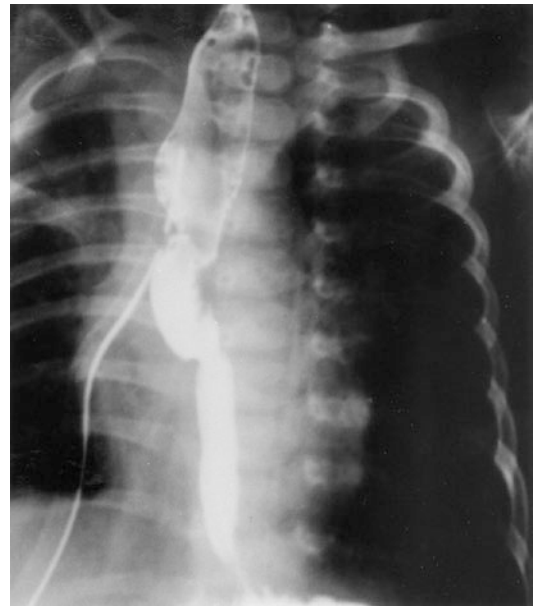

Fig. 21.4 Contrast study on the tenth postoperative day after delayed primary repair showing an intact anastomosis

is present, the chest drain is removed, antibiotics are discontinued, and the patient is allowed to take feedings orally. Furthermore, regular chest physiotherapy is recommended to avoid respiratory infections.

Complications

In most studies, the survival rate for patients with esophageal atresia after delayed primary anastomosis is reportedly greater than 90 % [23, 29, 34, 38, 41, 44,46–54]. The early complications after delayed primary anastomosis are leaks, which occur in up to 50 % of patients [22, 23, 34, 35, 37, 41, 43, 44, 46–48, 50, 51, 55–58]. Most anastomotic leaks are minor and subside spontaneously on total parenteral nutrition without the need for surgical intervention. However, some investigators have reported major disruption and failure of conservative management with need for drainage or reoperation in up to 15 % of their patients [46, 57]. Anastomotic strictures occurred in some studies in up to 80 % of cases [23, 35, 43]. The presence of a previous anastomotic leak has been found out to be the most important factor in stricture formation [28]. Most esophageal strictures respond to periodic dilatations, while some patients finally needed resection and reanastomosis [22, 23, 35, 36, 43, 48, 50, 51, 58, 59]. Persistent esophageal strictures occur mainly in association with gastroesophageal reflux [60]. Gastroesophageal reflux that is present after delayed primary anastomosis usually requires a more aggressive approach to treatment. According to most authors [22, 29, 34–38, 41, 43–50, 53, 55–59, 61], up to 30 % of their patients, treated by delayed primary anastomosis, require fundoplication in the first year after surgical repair of their esophageal atresia due to either symptomatic gastroesophageal reflux or persistent strictures. Severe esophagitis caused by gastroesophageal reflux occurs only occasionally after delayed primary anastomosis and usually can be resolved by fundoplication [45, 48, 55].

Long-Term Results

The majority of patients who have undergone delayed primary esophageal anastomosis are able to eat normally without dysphagia (Fig. 21.5). The reported incidence of swallowing difficulties is low [23, 41, 42, 58, 61]. Patients with dysphagia usually are found to have gastroesophageal reflux or reflux-associated strictures on contrast studies. Recurrent aspiration pneumonia is uncommon in patients who had delayed primary anastomosis but is reported by some authors [37, 42, 45, 61]. Failure to achieve a satisfactory delayed primary anastomosis of the esophagus with need for esophageal replacement is relatively rare and only necessary in a few patients [34, 35, 46, 58]. Long-term follow-up studies have shown that the majority of patients have normal growth and development curves after delayed primary anastomosis [36, 43, 56, 59]. However, the potential risk of Barrett's metaplasia highlights the need for continued long-term follow-up [36, 48].

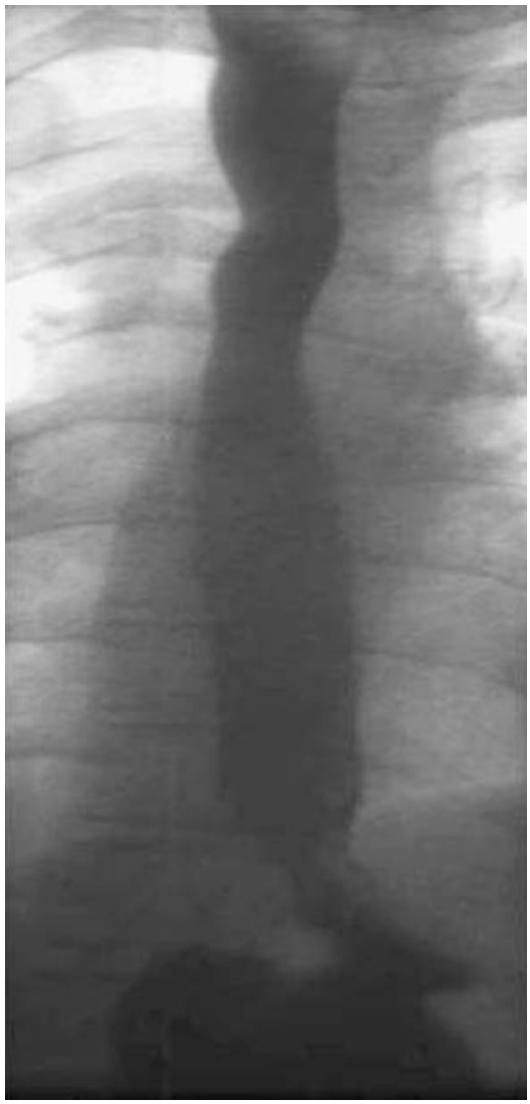

Fig. 21.5 Contrast study in the same patient showing a patent esophagus at 16 years of age

Conclusion

Delayed primary anastomosis provides an excellent postoperative outcome with good long-term functional results. The high incidence of gastroesophageal reflux and associated morbidities requires early intervention to prevent ongoing feeding problems due to strictures and esophagitis. Long-term follow-up is recommended because of the potential risk of Barrett's metaplasia.

The disadvantages of waiting for the esophageal segments to grow and hypertrophy are prolonged hospital stay and constant threat of aspiration pneumonia, which require continuous skilled nursing supervision. It may also be argued that the initial prolonged hospitalization is expensive. These factors must be balanced against reduced long-term morbidity in a child who should have a normal life expectancy and against the disadvantages of esophageal replacement. There is no "good" substitute for a child's own esophagus.

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22 Surgical Methods to Increase Esophageal Length in Long (Wide)-Gap Esophageal Atresia with and Without Tracheoesophageal Fistula

Sigmund H. Ein

Introduction and Philosophy

The long (wide)-gap esophageal atresia (EA) continues to be a problem for the pediatric surgeon; however, ingenious and interesting surgical attempts to bridge the gap continue to come forth. These new ideas are probably for 10–20 % of newborns/infants with EA who are not immediately suitable for primary anastomosis (15 % without a tracheoesophageal fistula (TEF), 5 % with a TEF).

In the 1950s through to the 2000s, several methods to elongate and eventually bring together both esophageal segments to overcome a wider than usual atretic gap have been employed with limited success; however, elimination of anastomotic tension, significant complications, morbidity, and prolonged hospitalization have not resulted [55]. "Many techniques have been proposed to obtain esophageal elongation; although all the procedures give acceptable results, none of them has been unanimously accepted by pediatric surgeons" [2]. "I think (they) got a raw deal, but that's often the fate of pioneers and innovators" [57].

In the following examples, most lengthening procedures focused on the usually bigger and better developed upper esophageal pouch; some on both esophageal segments and a few on the always small and poorly developed lower esophagus. As time passed from the first of these innovations in the 1950s, many of these authors and others used a combination of older and previously described novel techniques and/or their own newer procedure [6, 8, 24, 26, 50, 51]. All of these wide-gap EA patients, with or without a TEF, require some sort of surgery either to make the diagnosis of a wide gap and/or division of the TEF (right thoracotomy), esophagostomy, and always a feeding gastrostomy. Following this degree of stabilization came a succession of thought-provoking ideas, procedures, and options to bring about a primary (albeit delayed) esophageal anastomosis rather than an esophageal interposition, replacement, or substitution. The management of this relatively rare and difficult variation of EA will continue to demand an individualized approach and consideration of all of the various techniques that have been described.

Generally speaking, all of these procedures have the usual postoperative complications seen with the standard primary anastomosis, with, as in most large and complicated operative procedures, a significant learning curve [5]. In spite of the above trials and tribulations, the end results were fairly

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similar to the common esophageal repair, that is, a fairly reasonable, but not perfect, swallowing tube.

All of the authors seem to be in agreement with the philosophy that "…the best tissue for oesophageal reconstruction is oesophageal tissue" [5]. Otherwise, they wouldn't have gone through the effort of trying out their new ideas on "bridging the gap." However, it is interesting to note that, with few exceptions, most of these innovative procedures were seldom tried by the silent majority of pediatric surgeons and/or if they were seldom reported in the literature. Rehbein [38] concluded that "…it may not always be technically possible to achieve this but …it is a worthy goal at which to aim."

The hopes and aspirations of all of these innovative pediatric surgeons were best represented by Rehbein's words in 1971: "With children, the essential requirement is to establish a condition that will continue reliably trouble-free for decades. Direct uniting of the (esophageal) segments would appear to us to provide a better guarantee than a transplant. It well could be, however, that transplants in cases of esophageal atresia could become superfluous" [38]. It is interesting to review the writings of the above authors and see their ingenious ideas which they have published on these and other pediatric surgical problems.

Once again, these novel ideas enforce the teaching that the infant or child's own esophagus is almost always better than any substitute that can be made for it; so the search goes on.

This chapter reviews innovative attempts to join the two pieces of wide-gap EA together in three novel approaches:

1. Lengthen upper pouch
2. Pull/push upper and lower pouches together
3. Lengthen lower pouch

Upper Esophageal Segment Anterior Flap

Ten Kate [49] in 1952 first reported the ingenious use of an anterior flap of muscularis used to wrap around the esophageal mucosa to mucosa anastomosis. In his four cases, tearing of the upper-pouch mucosa gave trouble, which led him to suggest a muscle flap be used.

In 1981, this approach was modified by Gough [15] to bridge a wide gap between two EA segments that could not be connected by a primary anastomosis. His rationale was that the wide gap between the two esophageal segments can be reduced if, instead of opening the larger upper pouch at its most distal end, an anterior full-thickness flap could be fashioned and turned down (as an extension of the back wall of the upper segment) to be sewn without tension to the narrower back wall of the lower segment (Fig. 22.1). Then the wider upper esophagus could be closed anteriorly (without compromising its lumen) and sewn to the equally small lower esophagus (Fig. 22.2). The only drawback to this type of anastomosis is that it is three cornered. None of Gough's patients leaked but they all required dilatation.

Davenport [5] concluded that "…the flap will provide sufficient tissue to bridge longer defects at least equivalent to the height of up to four vertebral bodies." However, he did admit "Our less than acceptable complication rate in the first part of the series would lead us to advise care and caution in learning and applying a new technique." This flap technique has not produced many papers since its inception.

Circular and Spiral Myotomy

In 1969, Livaditis et al. [32] introduced the operation of circular myotomy as an effective means of bridging a particularly wide gap in EA to enable a primary anastomosis.

In laboratory studies, he showed that esophageal peristalsis is normal up to and beyond the circular myotomy and the myotomy causes no functional impairment of swallowing [33]. The myotomy site heals with a thin layer of fibrous tissue rich in elastin, and the mucosa at the level of the myotomy distends in response to increased intraluminal pressure. The myotomy does not cause stricture of the mucosa, nor ischemic necrosis and fibrosis of the esophagus distal to the myotomy [33].

An interesting addition to the circular myotomy is the possibility of doing more than one myotomy on a longer than usual upper pouch, a circular myotomy on a longer than usual lower pouch [9, 14], and/or myotomies on both segments [30]. In

the case of an upper pouch that is too short to have a myotomy made with ease, the upper pouch can be brought out the right neck, the myotomy done, and then the upper pouch replaced into the mediastinum for the anastomosis [22, 27]. Each myotomy adds 1–1.5 cm (equal to 1 vertebral body) to the length of the esophageal segment [42, 55].

There is almost always seen an outpouching of the mucosa at the myotomy site, but this rarely created a clinical problem [22]. However, there has been a report of two patients who had a subsequent history of impaction of solid food particles in the upper esophageal segment at the age of 13 months and 2 years. Whether this was due to the dilated and dysfunctional upper esophagus at the circular myotomy site or the more common holdup at the anastomosis is open to speculation. The authors of this report suggested that "the possibility that the circular myotomy contributed to this increased incidence of impaction is raised" [47]. Of course, there is always a risk of making a hole in the mucosa, but as long as it is recognized and repaired at the same time, it seldom causes a problem. This lengthening procedure adds no increased morbidity to the usual list of primary EA repair complications.

As with each new idea, someone comes up with an equally novel approach to change the new idea. Therefore, in 1976, Eraklis et al. [7] modified this technique by having the anesthesiologist insert a balloon catheter down the esophagus to facilitate the myotomy and decrease the risk of entering the lumen.

In 1983, Schwartz [42] suggested that the myotomy was easier to do over an inflated No. 8 French Foley catheter, which the surgeon passed through a purse-string suture placed at the tip of the proximal esophagus (Fig. 22.3).

In 1987, to this innovation, Kimura et al. [26, 27] added a spiral myotomy which he said was mandatory to do over the inflated Foley catheter and was done by twisting the esophagus two and one half revolutions, deflating the Foley balloon, stretching the spiraled myotomy with moderate tension, and then sewing the muscle edges together (Fig. 22.4). The spiral myotomy gives an elongation of 2 cm and the sutured edges prevent a mucosal tear.

In a similar fashion with all the other innovative ideas and procedures, only a few series of circular myotomies have been reported, but each series had only a handful of cases [27, 42, 45–47]. "The circular or spiral myotomy is still the most commonly used technique to lengthen the esophagus in the repair of long gap atresias" [2].

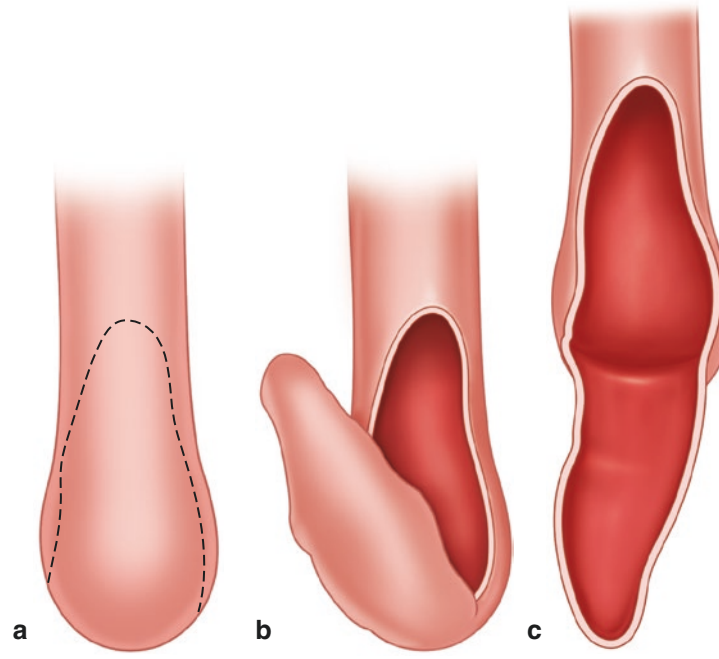

Fig. 22.1 Long, wide, full-thickness posterolateral esophageal pedicle flap 1-3 cm long from the dilated upper pouch (**a**) The posterior flap is mobilized (**b**) until it reaches downward without tension (**c**) (With permission from Dr. Adrian Bianchi (*Pediatr Surg Int*) (Ref. [5]))

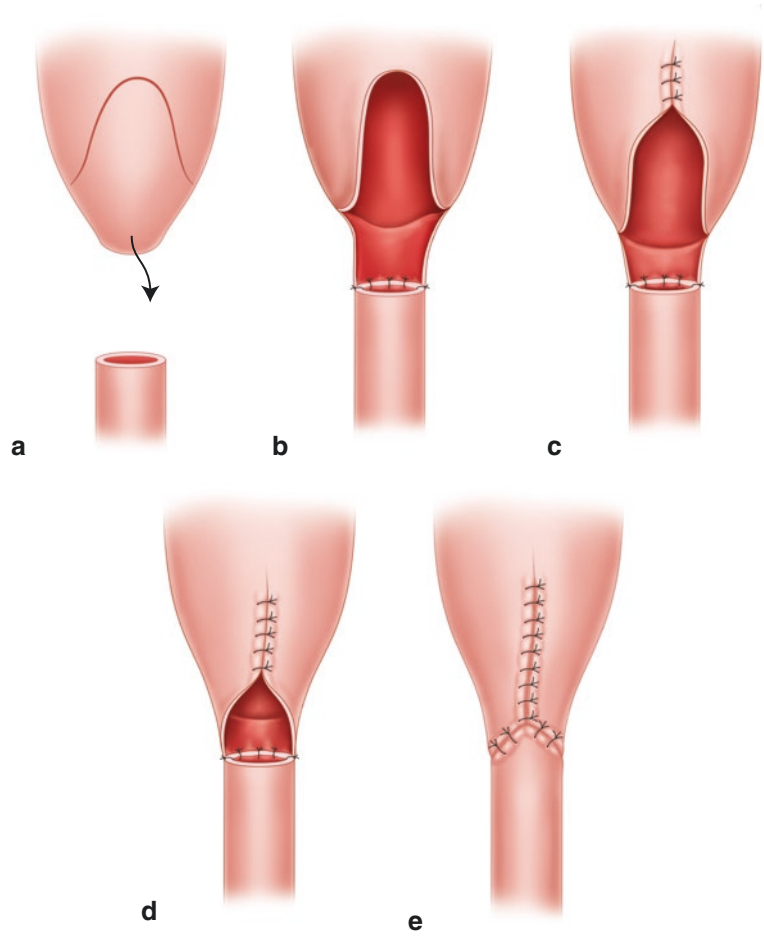

Fig. 22.2 The line of the incision for the anterior wall flap from the upper esophageal pouch is marked (**a**), and the *arrow* shows the downward direction of the flap, which is sutured to posterior wall of the lower esophageal segment (**b**). The anterior wall defect of the upper pouch (from the flap) is repaired (**c**) down to the lower esophagus (**d**), which is then closed in the usual transverse fashion (**e**) (With permission from Elsevier Publishing (*J Pediatr Surg*) (Ref. [15]))

Suture Fistula

In 1971, Rehbein and Schweder [38] apparently initially proposed the idea of pulling (after bougienage had failed in some patients) two widely spaced EA ends (proximal and distal) together in the anticipation of creating a fistula between the two ends. This fistula, it was hoped, would be able to be dilated either directly from above or via a string passed from the nose down through the now patent esophagus and out a feeding gastrostomy. At a later date, if this stricture cannot be maintained open and wide enough to tolerate normal fluid and solids, it could be resected.

Rehbein and Schweder [38] did the above in three stages:

1. The gap was bridged by introducing a silver prosthesis to which both segments were attached. In about 2 weeks the gap was overgrown by fibrous tissue, the prosthesis had become sufficiently detached to enable to be withdrawn through the gastrostomy (Fig. 22.5).
2. A nylon thread was introduced into each segment with the ends emerging through the nose and gastrostomy. The two esophageal segments were approximated as far as possible by three sutures. Four weeks later, using the thread, two silver olives were introduced both from above and pushed up from the gastrostomy and pressed together crushing the two blind ends of the esophagus between them. Thirty-six hours later a channel (between the two segments) was created (Fig. 22.6).
3. A thread was passed through both esophageal segments which were approximated as far as possible by three sutures (Fig. 22.7).

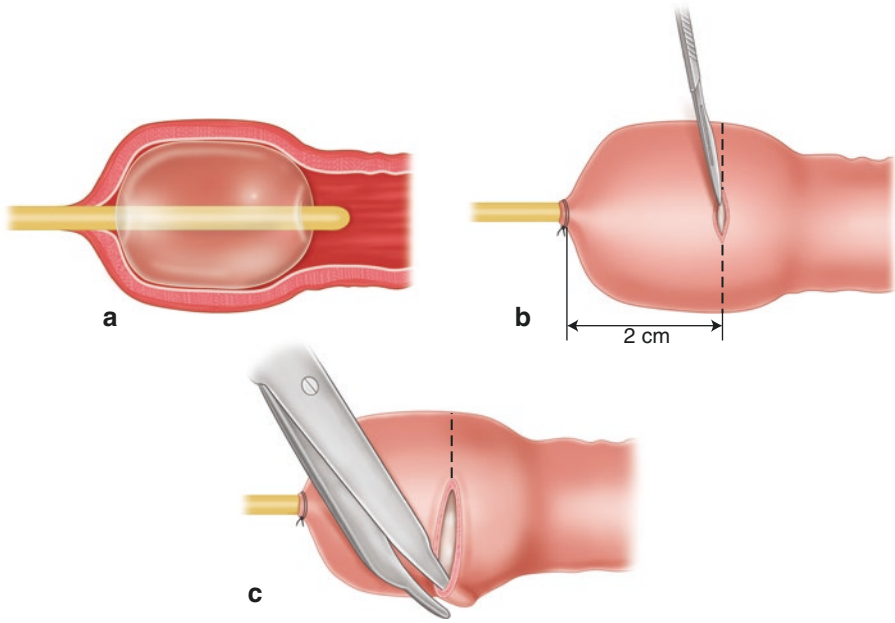

Fig. 22.3 The Foley balloon is passed into the end of the esophageal segment and the balloon is inflated (**a**). The myotomy is begun with a scalpel 2 cm from the end (**b**), and the esophageal muscle is divided with scissors (**c**), after a plane of dissection between the muscle and submucosa is identified. The completed myotomy yields 1–1.5 cm of extra length (With permission from Elsevier Publishing (*J Pediatr Surg*) (Ref. [42]))

It was Rehbein's conclusion that "even major (2 cm) esophageal defects are actually bridged along a prosthesis that is introduced temporarily. The fibrous canal, which develops around such a prosthesis or around a perlon (nylon) thread, shrinks in a longitudinal direction and draws the segments toward each other. At the same time, this shrinkage causes constriction and makes subsequent bougienage necessary. If the constriction does not yield, it will have to be resected at a later date" [38].

In 1974, Shafer and David [43] tried the same suture fistula technique as Rehbein, in which he used silk instead of nylon. He claimed: "Rehbein's technique should be attempted when the two ends can be almost but not quite approximated." Very few papers have been published on this technique.

Electromagnetic Bougienage

The original idea for bougienage was described in 1965 by both Howard and Myers [21] and Johnson [23] who introduced manual bougienage for the upper pouch to elongate it and accomplish a delayed primary anastomosis.

As with all of the other innovations, in 1975 Hendren and Hale [18] modified Howard's simple technique, this time using a surgical approach. He reported two cases of wide-gap EA in which "intermittent electromagnetic force was used to pull together metal bougies ("bullets") placed in each esophageal end and electromagnetic field was then used to pull the bullets together. This method elongated and enlarged the esophageal segments enough to accomplish their anastomosis later" [18].

Hendren's first two successful cases were reported in 1975 [18] and in 1976 he reported two more after "certain refinements in the method were developed" (Fig. 22.8) [19].

1. The sump suction tube attached to the upper-pouch bullet was brought out through a lateral pharyngotomy instead of the nose.
2. The stem of the lower-pouch bullet was brought through a small separate stab incision in the midline to direct it straight upward into the lower esophagus. When it was previously brought through the same opening as the gastrostomy tube site, there was troublesome leakage.

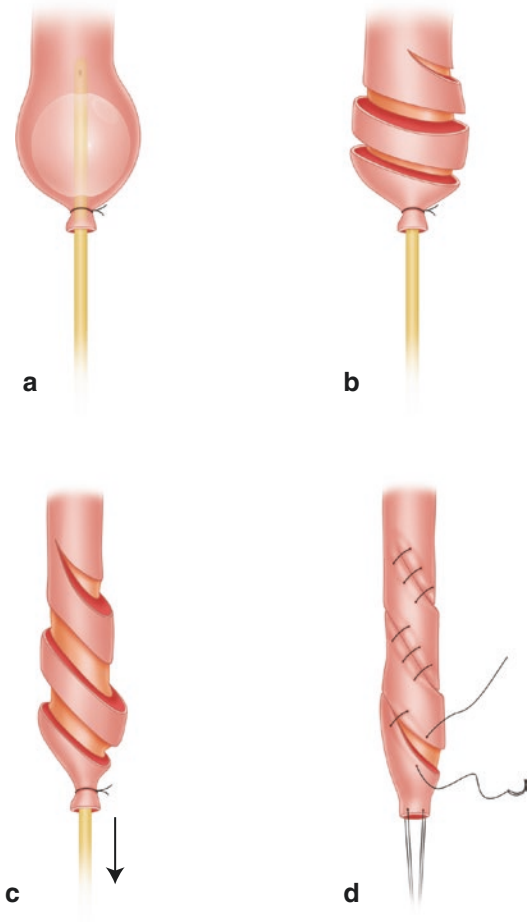

Fig. 22.4 An eight French Foley catheter is passed through the end of the esophageal segment and the balloon inflated (**a**). A spiral myotomy is made over two and one half revolutions (**b**), the balloon is deflated, and the esophagus is twisted and stretched with moderate tension (**c**). The muscle edges are then sutured (**d**) (With permission from Elsevier Publishing (*J Pediatr Surg*) (Ref. [26]))

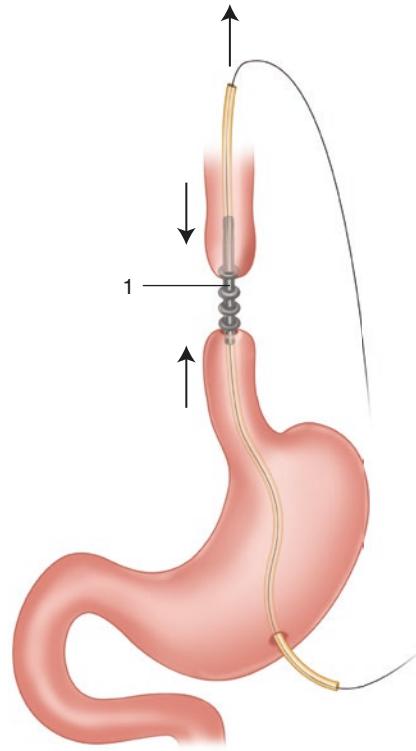

Fig. 22.5 The gap between the two esophageal segments is bridged by a silver prosthesis and the two segments connected with the prosthesis via a string passed down through the nose and out the gastrostomy (With permission from Elsevier Publishing (*J Pediatr Surg*) (Ref. [38]))

3. The lower-pouch bullet was placed "by feel" into the distal esophagus without requiring anesthesia.
4. The lower-pouch bullet, which has a flexible steel stem, was placed by sliding a rigid metal tube over the flexible cable, using this as a handle to direct the bullet up into the lower esophagus [19].

Bougienage consisted of alternating magnetic force (on for 60 s and off for 60 s) with the force building for 15 s and maintained at full force for 45 s, followed by a 15 s decrease and 45 s off. The bougienage continues at a rate of 30 times per hr. The force of pull is adjusted to be less than what seems to cause the baby discomfort by observation. These babies were prone to respiratory difficulties during the first few weeks of life, so its use was deferred until 1–2 months of age, when gastrostomy feeds are well underway. Furthermore, Hendren raised several questions: (1) cost of the electromagnetic machine, prolonged hospitalization, and close nursing supervision; (2) in communities where machine bougienage is not possible, upper and possibly lower-pouch stretching can be attempted for a few minutes several times daily, although it does not duplicate the hundreds of daily stretchings that are possible using the machine; and (3) the risk of whether magnetism may have an adverse effect on the baby. There was no evidence of untoward reaction to

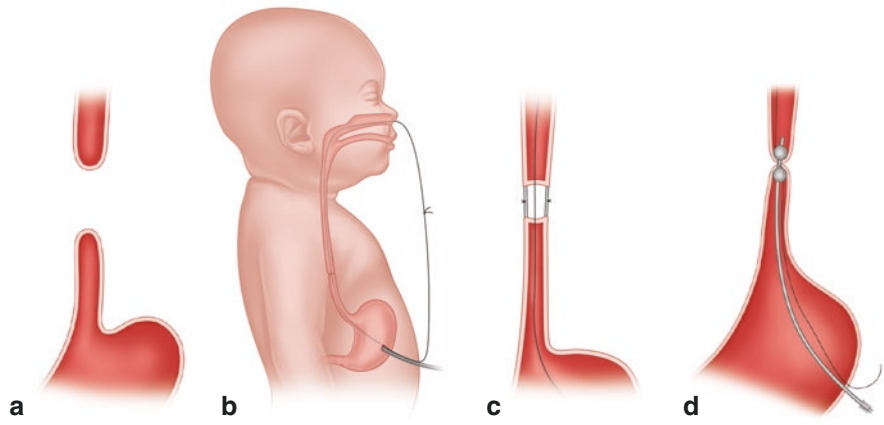

Fig. 22.6 Schematic picture of a long gap esophageal atresia with a long gap (**a**). A nylon thread is introduced into each closed esophageal segment, the ends emerging through the nose and gastrostomy (**b**). The two esophageal segments are approximated as far as possible (**c**) Four weeks later, a silver olive is introduced into each segment (**d**) and pushed together until the two blind ends are crushing (With permission from Elsevier Publishing (*J Pediatr Surg*) (Ref. [38]))

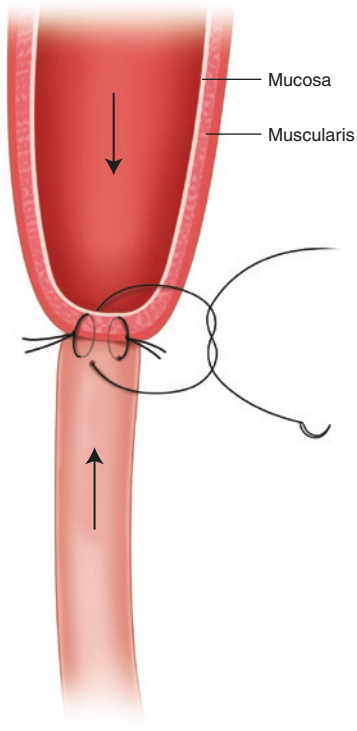

Fig. 22.7 Approximation of unopened upper esophageal pouch to the lower esophageal segment after division and closure of the distal TEF. The central silk suture penetrates the lumen of the upper pouch (With permission from Elsevier Publishing (*J Pediatr Surg*) (Ref. [43]))

magnetism in Hendren's four EA patients [19]. Bougienage in his four cases lasted between 30 and 60 days. It was observed that bougienage not only lengthens the two esophageal segments but induces considerable hypertrophy and a secondarily increased blood supply, thus permitting extensive mobilization with hypovascularity. There was also noted considerable inflammatory reaction in the mediastinum. As in other techniques, Hendren also suggested trimming the two esophageal ends, if possible, at the time of the anastomosis.

To this date, no other reports of electromagnetic bougienage for wide-gap EA have been reported. It is interesting, however, that there is a recent report of the use of magnets to repair pectus excavatum [16, 17] and to create a bowel anastomosis [36].

Staged Esophageal Lengthening with Internal and External Traction Sutures (Foker Growth Procedure)

Between 1984 and 2004, Foker et al. [12] treated 38 patients who presented with the longest gap EA with internal and external traction sutures which quickly and successfully produced esophageal growth for a primary repair (Fig. 22.9) [11, 13].

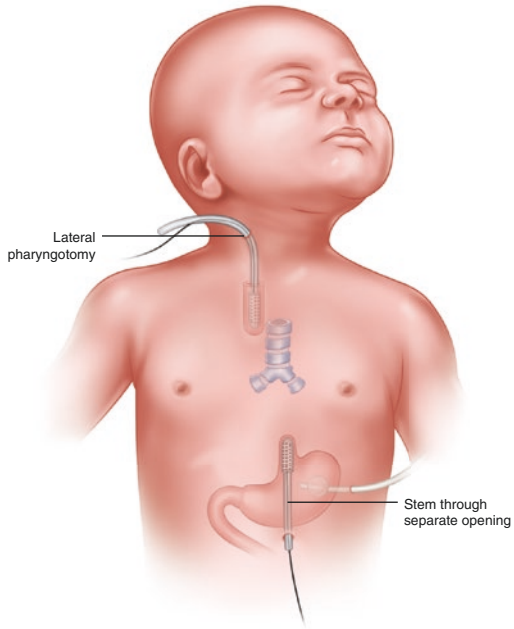

Fig. 22.8 1976 modifications to electromagnetic bougienage. Sump suction tube attached to the upper-pouch bullet is brought out through a lateral pharyngotomy instead of the nose; the stem of the lower-pouch bullet is brought through a small separate gastrostomy (instead of beside the tube gastrostomy) in the midline. It is placed by sliding a rigid metal tube over the flexible cable, using this as a handle to direct it straight upward into the lower esophagus "by feel" (With permission of Elsevier Publishing (*J Pediatr Surg*) (Ref. [19]))

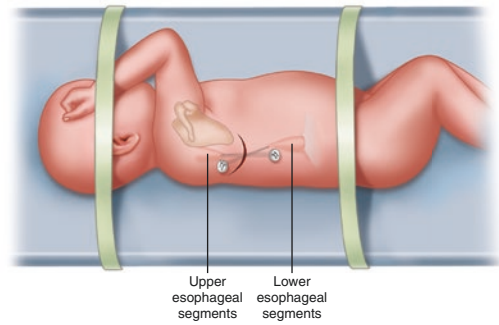

Fig. 22.9 A smaller than normal (3 cm) EA repair 3 cm right fourth to fifth intercostal space thoracotomy incision is made sparing the serratus anterior muscle. Two intercostal entries are made between the fourth and seventh interspaces. A transpleural approach is made. Four pledgeted traction sutures (deep bites, but not into the lumen) are placed into each esophageal segment, and these sutures are brought out posteriorly onto the chest wall; the upper segment sutures exit below the thoracotomy incision and the lower segment sutures above. Traction is placed on the segments by threading the sutures through silastic buttons on the skin surface (With permission from Elsevier Publishing (*Semin Pediatr Surg*) (Ref. [12]))

Throughout the 25 years since this novel technique was first proposed by Foker, there has been continuing doubt about the feasibility and actual results of this double suture traction approach. Following his 1997 presentation, one pediatric surgeon said: "We pediatric surgeons have learned that a primary anastomosis of the esophagus must not be tried when the gap is greater than 2.5 cm, dictated by trial and error and 'common sense'. Dr. Foker and his colleagues have challenged our common sense gap length that has been achieved during our experience for the last 50 to 60 years" [11]. Another Pediatric Surgeon said: "I must say I enjoyed Dr. Foker's presentation, and I think that during the years I have learned not to be skeptical of individuals who do things differently from accepted methodologies" [11].

In a 2009 survey of 88 pediatric surgeons about "The Surgical Approach to Esophageal Atresia Repair and The Management of Long-Gap Atresia," the authors concluded that "Even among experts, there is little consensus on the definition of or the optimum technique for repair of long-gap EA" [39]. Having said that, the same survey revealed that "gastric interposition is the most preferred technique for long-gap EA when primary anastomosis is not possible with 94 % of those surgeons who use the technique are satisfied with it. Growth of the esophageal ends by traction is the other major technique used, but only 76 % of surgeons who use it are satisfied with it" [39]. Suffice it to say, of all the bright, new, novel, ingenious ideas to bridge the long-gap EA and create a successful anastomosis (with as many postoperative problems as other easier primary anastomoses and/or esophageal replacements), the Foker Growth Procedure, after years of disbelief and criticism, seems to be the one technique that more pediatric surgeons are trying (and successfully so) than all of the others put together [34]. As Foker said, when he ended the

question and answer period after his 1997 presentation: "The esophagus serves the child well, much better than the alternatives" [11]. As expected, this is now being done by thoracoscopic means [53].

Extra-thoracic Esophageal Elongation Procedure

In 1994, Kimura and Soper [25] developed a scheme of multiple extra-thoracic esophageal elongation procedures for managing patients with long-gap EA by staged translocations of the proximal esophagostomy stoma down the anterior chest wall gaining 2–3 cm each time. Each elongation can be staged at any time but is usually done at 2–3 months intervals with one to five elongations over time. The definitive esophageal reconstruction has been done as late as 24 months of age.

The esophagostomy is best made on the right side just above the clavicle and tunneled subcutaneously over the clavicle and down the anterior chest wall (Fig. 22.10). Each elongation procedure has an eight French Foley catheter placed into the esophagus through the stoma, its balloon inflated and the esophagostomy closed around the catheter by a purse-string suture. The skin overlying the subcutaneous esophagus is opened in a zig-zag fashion to avoid scar contracture when it is permanently closed. The stoma and proximal esophagus are mobilized all the way up to the cricoid cartilage using the electrocautery minimally. The mobilized proximal esophagus is then passed subcutaneously distally for a few cm, fixing the distal portion of the elongated esophagus to the anterior chest wall fascia to take tension off the new stoma. The continuous movement of the infant/child's neck contributes to further elongation of the proximal esophagus. The elongated esophagus has its muscular continuity preserved, which may be advantageous for its motility. Even though the blood supply in the proximal esophagus originates proximally and travels in its submucosa, and vascular maturation can be expected while the esophagus is embedded in the subcutaneous tunnel, the distal portion of the elongated esophagus still tends to become somewhat ischemic, scarred and usually requires resection of a few cm before anastomosis. Saliva and the sham-fed liquids captured in the esophagostomy appliance can be re-fed into the gastrostomy tube. Finally, esophageal reconstruction is indicated when both ends of the unattached esophagus are at the same vertebral level on a lateral chest x-ray. This is usually seen when the subcutaneous proximal esophagus is at the xiphoid process [27]. This long, somewhat complicated procedure has rarely been reported in any series since its original presentation [48].

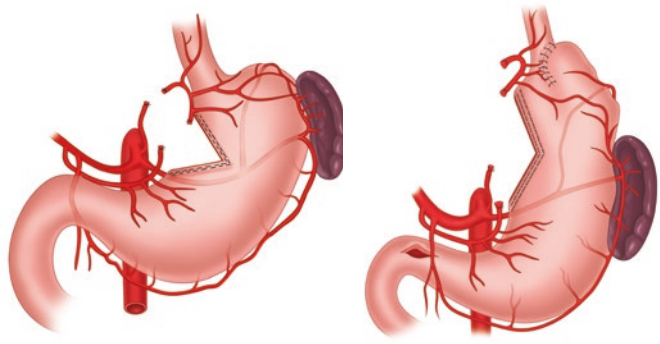

Fig. 22.10 Ligation of the left gastric artery is followed by division of the lesser curvature of the stomach using a GI stapler. The length of the incision on the lesser curvature provides a twofold lengthening of the cardia and distal esophagus. Fundoplication (partial wrap) restores the angle of Hisand prevents GER. Pyloromyotomy or pyloroplastyimproves gastric emptying (With permission from Springer Publishing (*Pediatr Surg Int*) (Ref. [41]))

Elongation of the Distal Esophagus with a Gastric Tube

In 1968, Burrington and Stephens [3] reported a 2.5-month-old baby with a wide-gap pure EA who had her atretic lower esophagus replaced with a so-called partial gastric tube (GT) (a true esophageal interposition) which was distally based (antiperistaltic) on the greater curvature of the stomach and then passed up through the esophageal hiatus. Since only the lower half of the esophagus is missing and needs replacement, half the usual length of GT is required, involving only half of the greater curvature. Frequently, there is a small atretic but still useable distal esophagus which can be part of an isoperistaltic GT. This entire procedure involves an Ivor-Lewis abdominal and right thoracic approach. The small distal esophagus can be anastomosed to the proximal esophagus with more ease than the GT; however, it is often somewhat devascularized because its blood supply comes up from the stomach. GER also comes up from the stomach, and this can cause distal esophagitis leading occasionally to a Barrett's esophagus [31, 44]. Stomach, [41] colon [37], and jejunum [1, 40] have also been similarly used as an esophageal interposition (as above) with equally good results.

Elongation of the Lesser Curvature

In 1992, Schärli [41] published a new means for the preservation of the distal esophagus and cardia, because mobilization of the distal esophagus alone is possible only to a limited extent, due to the fixation of the lesser curvature of the stomach and the left gastric artery. He showed that ligation of the left gastric artery and transverse diagonal division of the lesser curvature with a stapler permits mobilization of 6–8 cm of distal esophagus with preservation of the cardia, ensuring that primary anastomosis of the two esophageal ends is possible (Fig. 22.11). An incision of 3 cm in the lesser curvature provides a gain of 6 cm in length. The esophageal anastomoses were intrathoracic and cervical, and the retrosternal space was also used. In all of his five patients, a semi-fundoplication was performed as well as a pyloroplasty.

Further reports of this procedure (other than Schärli) are not easy to find, although Schärli's

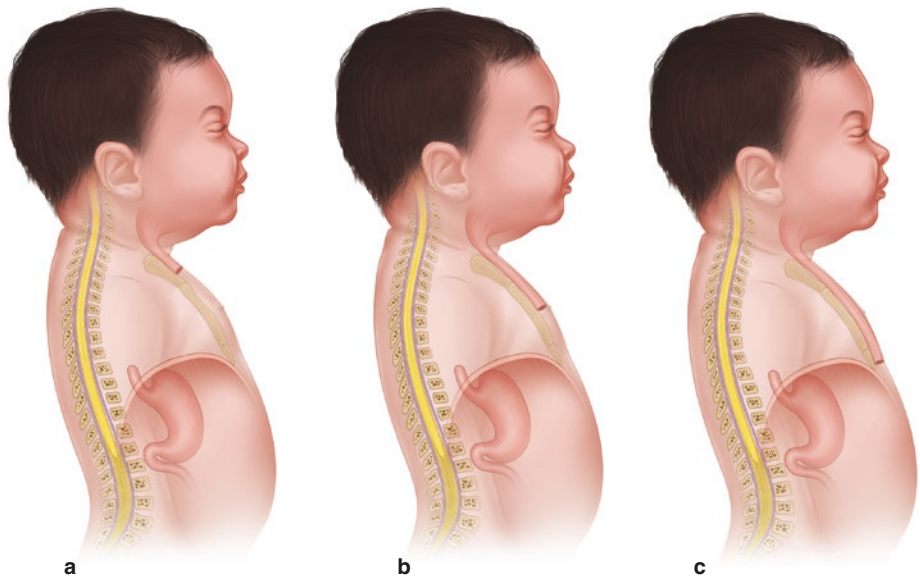

Fig. 22.11 The esophagostomy is best made on the right side just above the clavicle and tunneled subcutaneously over the clavicle and down the anterior chest wall. Each stage (usually 1–5) usually gains 2–3 cm each time (With permission from Elsevier Publishing (J Pediatr Surg) (Ref. [25]))

five patients did well. Once again, a novel approach remains hardly used or copied [10, 54].

Application of Collis Gastroplasty to the Management of Wide-Gap Esophageal Atresia

In 1995, Evans [8] described the use of the Collis gastroplasty as an esophageal lengthening technique for the distal esophagus. This procedure creates a gastric tubular segment from the lesser curve of the stomach (Fig. 22.12). It was felt that this procedure at least doubles the length of the lower esophagus. It is also suggested that an antireflux procedure and pyloroplasty both be added to the Collis gastroplasty to eliminate (or minimize) the GER that is associated with at least 85 % of EA patients [24, 35]. The usual and similar postoperative complications occur with this lengthening procedure as with the others, except the antireflux procedure often causes a partial obstruction at the hiatal area [24]. Therefore, a loose fundoplication may be better for avoiding swallowing difficulties. Furthermore, the influence of the gastric juice secreted from the new tubular gastric segment on the esophageal mucosa above it cannot be ignored [24].

As with the other surgical alternatives, the results of this distal esophageal lengthening procedure, done in wide-gap EA babies in other series, have occasionally been reported by others [4, 24]. Therefore, it must be assumed that it has not been used very often.

Elongation of the Distal Esophagus by Stretching

It appears that Lafer and Boley [29] was the first to report a technique for elongation of the distal EA in 1966. This was, again, an expansion of the previously published papers by Howard and Myers [21] and Johnson [23] both in 1965, in which the upper pouch was elongated, eventually enabling a primary anastomosis of the two pieces of atretic esophagus. Initially, Lafer and Boley [29] removed the feeding gastrostomy and a Hegar sound was passed under x-ray control into the distal esophageal pouch. Intermittent pressure was then applied for 5–10 min, the sound removed, and the gastrostomy tube reinserted. This procedure was continued three times weekly, initially with x-ray control, but eventually at the bedside with minimal obvious trauma to the infant, and with surprising ease. While the proximal pouch was also stretched at the same inter-

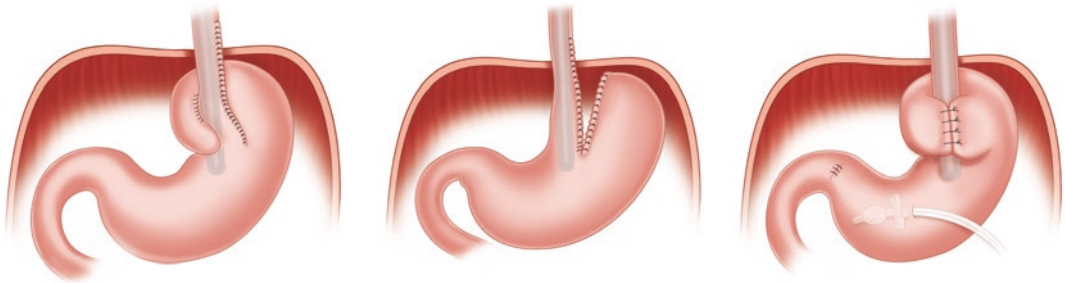

Fig. 22.12 Standard Collis(-Nissen) procedure. Vertical gastroplasty is created with staplers parallel to the lesser curve of the stomach with a bougie in the esophagus. The fundoplication (Nissen) is wrapped loosely 360° around the tubular gastric neo-esophagus. Heineke-Mikulicz pyloroplasty is added for increased gastric emptying to minimize GER and also if vagal nerve damage is a possibility. The tube gastrostomy remains (With permission from Dr. Hisayoshi Kawahara (*World J Surg*) (Ref. [24]))

vals with a mercury bougie, most of the length was obtained in the distal pouch.

As with other previously described innovative surgical techniques in this chapter, clever modifications continued to arise in attempt to make the dilatation of the distal atretic pouch easier. In 1989, Kleinman et al. [28] showed that distal esophageal pouch growth could be achieved by producing intermittent hydrostatic stretches. This was done infusing dilute isotonic contrast into the distal esophageal pouch under fluoroscopy, after an angiographic balloon catheter was inserted through the gastrostomy to temporarily occlude the GE junction.

In 1989, Todd et al. [52] closed the GE junction with Teflon strips in an unstable, very low birth weight premature baby with EA and a distal TEF to prevent reflux into the trachea. This produced a patulous distal esophagus. On the other hand, it has been known for a long time that the small stomach of a pure EA baby can be dilated up (for an eventual GT replacement) by bolus gastrostomy feeds which, because of the known GER that is present in most EA, will also dilate up the atretic distal esophageal pouch.

In 2003, Hikida et al. [20] also reported elongation of this distal esophageal pouch by mechanical bougienage. Yet another novel idea to achieve the same result was published in 2006 by Vogel et al. [56]. A balloon catheter was placed beside the gastrostomy and its tip was positioned in the distal esophageal pouch (Fig. 22.13). The balloon was inflated and an elastic vessel loop was doubly wrapped around the gastroesophageal (GE) junction to secure the catheter in the distal esophageal pouch; the vessel loop was exteriorized through a separate abdominal stab incision. The authors "pressurized" the distal esophageal pouch for 1–2 h two to three times daily, but the original balloon catheter and vessel loop were soon dislodged and only the balloon catheter was replaced and inflated. Routine infant formula boluses were then administered retrogradely through the balloon catheter into the distal esophageal pouch to promote hydrostatic stretching. This routine was successful after just 2 weeks.

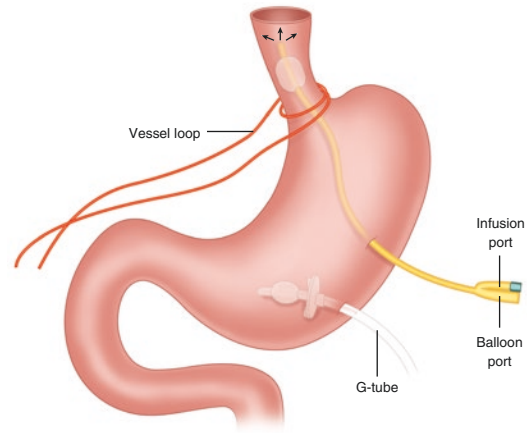

Fig. 22.13 The balloon catheter is placed beside the gastrostomy and its tip is positioned in the distal esophagus. The balloon is inflated and held in place by an elastic vessel loop doubly wrapped around the gastroesophageal junction. The distal esophageal pouch was then pressurized with a simple hydrostatic column of saline (With permission from Elsevier Publishing (*J Pediatr Surg*) (Ref. [56]))

The more one looks at all these variations of the same process, the simpler one seems easier and better, going right back to the original procedure by Lafer in 1966 [29].

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Thoracoscopic Repair of Pure Esophageal Atresia

23

Benjamin E. Padilla and Marcelo Martinez-Ferro

Introduction

Esophageal atresia (EA) is a congenital condition characterized by discontinuity of the esophagus. EA is a spectrum of anomalies. The vast majority of EA communicate with the tracheobronchial tree through a tracheoesophageal fistula (TEF). Pure EA without TEF requires special consideration because unlike other forms of EA/TEF, the long distance between the esophageal pouches often precludes primary anastomosis.

The incidence of EA is approximately one in 4,000 live births, with one third of cases occurring in premature infants. While overall survival for infants with EA/TEF exceeds 90 %, most deaths occur in babies with severe associated congenital anomalies. According to the "Rule of Halves," half of patients with EA have associated anomalies and half of these anomalies are congenital cardiopathies. Among patients with associated malformations, half have more than one malformation, mainly anorectal, urogenital, and skeletal. Additionally, malformative associations such as VACTERL (Vertebral defects, Anal atresia, Cardiac anomalies, TracheoEsophageal abnormalities, Renal and Limb disorders) and CHARGE (Coloboma, Heart defects, Atresia of the choanae, developmental Retardation, Genital hypoplasia, and Ear deformities) as well as trisomy 18 and 13 are relatively frequent. Therefore, genetic evaluation may be important at the time of deciding the surgical procedure in such cases [1].

The exact etiology of EA is unknown. Separation between the trachea and the esophagus is complete by gestational day 36. It is in this early gestational period that tracheoesophageal malformations develop. There is speculation that the etiology of EA/TEF in the absence of additional malformations is different from EA/TEF when associated with other malformations. Furthermore, while there are reports of EA in siblings, monozygotic twins, and in the offspring of individuals with EA/TEF, no clear pattern of inheritance has been identified [2, 3].

EA/TEF should be suspected in any newborn with choking or excessive drooling. Babies with EA swallow normally when fed, but gag and cough as the fluid refluxes through the nose and mouth. Over time, respiratory distress develops

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as a result of repeated aspiration. When EA is suspected, an orogastric tube is gently passed into the esophagus. The tube should pass into the stomach without any resistance and return gastric contents. If resistance is encountered or there is any doubt as to the position of the tube, a plain radiograph should be obtained (Fig. 23.1). There are case reports of perforation of the retropharynx or esophagus that were misdiagnosed as EA because the tube was lodged in the posterior mediastinum and could not be advanced [4].

The diagnosis of EA can be corroborated with a barium esophagram that shows contrast in a blind-ended esophageal pouch and no contrast in the stomach. Hyperosmotic water-soluble contrast should be avoided because of the concern for aspiration pneumonitis.

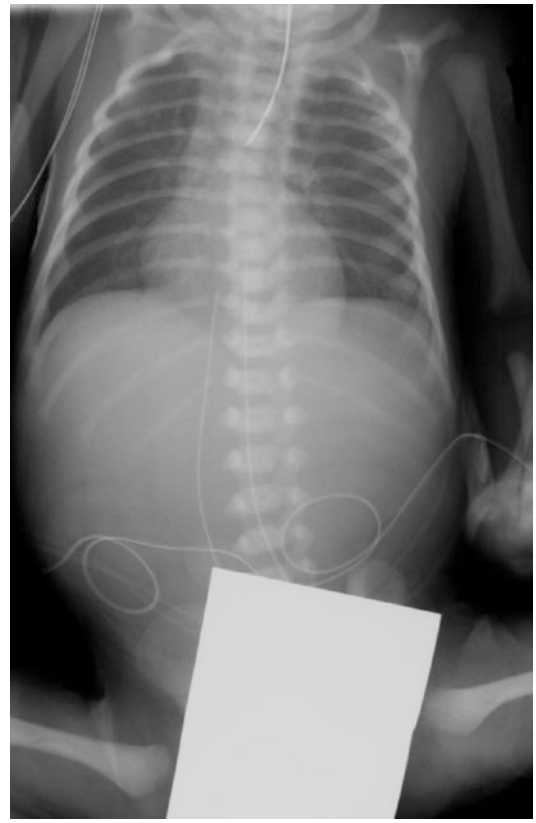

Fig. 23.1 This newborn has the classic radiograph for isolated esophageal atresia. Note the esophageal tube cannot be passed further than the proximal esophagus and there is no air in the abdomen

Isolated Esophageal Atresia

Isolated EA without TEF is the second most common type of EA, accounting for 5–7% of all patients with EA. Due to the long distance between the two blind-ending esophageal pouches relative to other types of EA, isolated EA is often referred to as "long-gap" EA. The terms "isolated," "pure," "type A," and "long-gap" EA are used interchangeably in the literature and refer to the same clinical entity. Strictly speaking, "long gap" should refer to any EA in which the distance between the atretic esophageal ends prevents a primary anastomosis [5]. As such, types B, C, D, and E can be considered "long gap" provided the distance between esophageal segments precludes a primary end-to-end esophago-esophagostomy. The exact distance that constitutes a "long gap" is controversial because of variation in the methods used to determine the gap length [6].

Unlike other types, the diagnosis of pure EA is often made during pregnancy. The characteristic prenatal sonographic findings are a small or absent fetal gastric chamber and associated maternal polyhydramnios. In contrast, fetuses with EA and distal TEF usually have a normal prenatal sonogram because the TEF prevents the formation of marked polyhydramnios. When EA is suspected, genetic testing should be performed to exclude chromosomal abnormalities, and fetal echocardiography is used to identify associated cardiopathies.

Typically, the newborn with isolated EA has an excavated abdomen because air cannot pass into the gastrointestinal tract. In the delivery room, the diagnosis of EA is confirmed by placing a radiopaque catheter in the esophagus until resistance is encountered. Plain radiographs show the tip of the catheter in the upper esophageal pouch. In cases of isolated EA, there is a complete absence of gas in the upper gastrointestinal track (see Fig. 23.1), while EA with distal TEF has gas in the stomach and bowel due to the fistula connecting the airway to the distal esophageal pouch. If the diagnosis is unclear, the surgeon can instill 2–3 cc of barium into the catheter and perform an esophagogram under fluoroscopy, taking care to aspirate the contrast material after the study to prevent

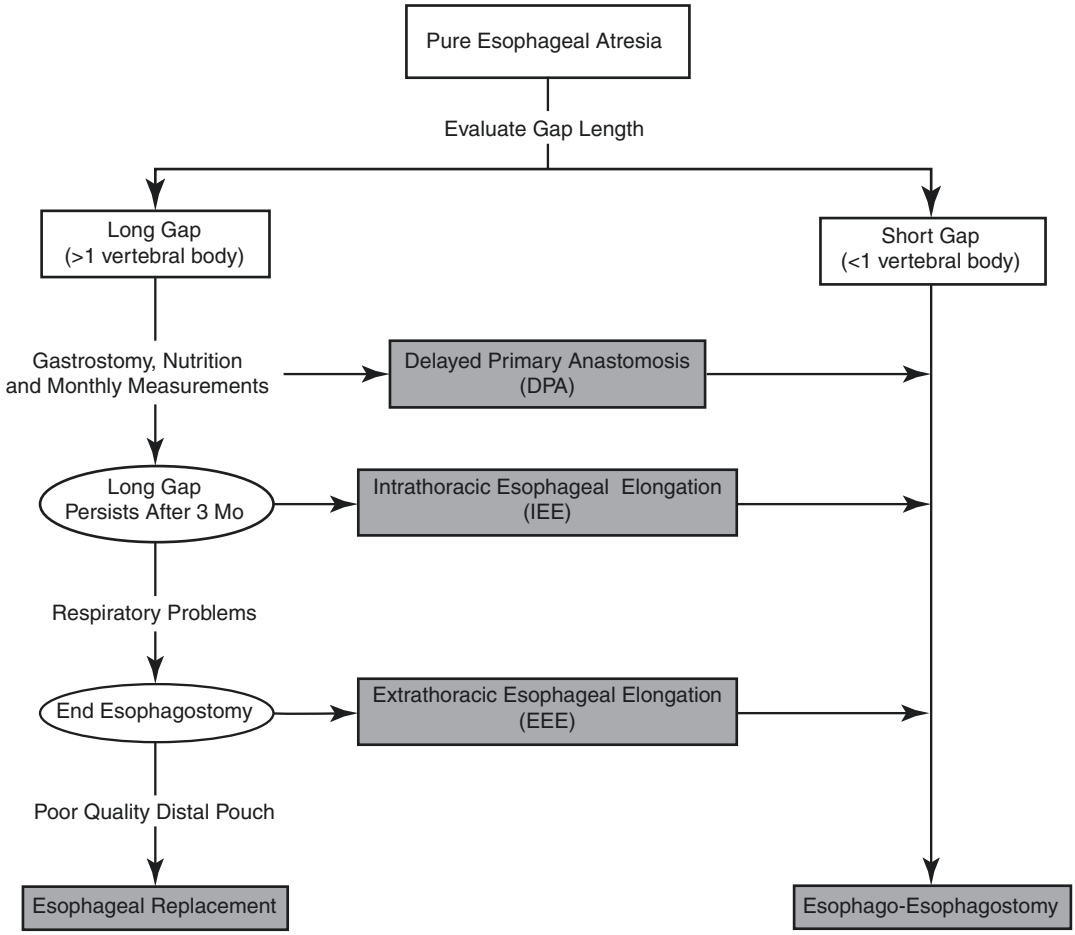

Fig. 23.2 Algorithm for the management of the baby with isolated esophageal atresia

aspiration pneumonia. Contrast esophagography often fails to demonstrate a TEF to the proximal esophageal pouch when it is present and never shows a distal TEF. Therefore, preoperative bronchoscopy is routinely performed to look for a TEF. Vascular rings and other causes of extrinsic compression should be sought to determine the most appropriate operative approach.

Management Options

The ideal treatment for EA remains controversial. Given the rarity of isolated EA, there is little consensus as to the best operative approach because individual and institutional experience in treating the disease is limited. Nevertheless, most surgeons agree that the native esophagus is the best conduit for esophageal function. Based on this principle, several techniques have been developed to elongate one or both ends of the atretic esophagus by means of an internally or externally applied traction device. Irrespective of the timing of operation and the mechanism of esophageal elongation, at the Fundación Hospitalaria Private Children's Hospital, we prefer the thoracoscopic approach when repairing EA and have shown it to be safe and effective. Furthermore, the thoracoscopic approach decreases postoperative pain, shortens hospital stay, and improves the cosmetic appearance [6, 7].

We propose a treatment algorithm based on the patient's anatomy and available surgical

options (Fig. 23.2) [8]. There are three principle considerations regarding the patient's anatomy: (i) What is the length of the esophageal gap? (ii) Is the long gap due to a short proximal pouch, a short distal pouch, or both? (iii) Does the patient have an esophagostomy? Surgical options include (i) delayed primary anastomosis (DPA), (ii) intrathoracic esophageal elongation (IEE), (iii) extrathoracic esophageal elongation (EEE), and (iv) esophageal replacement (ER).

According to the proposed algorithm, an isolated EA with a relatively short distance between proximal and distal pouches (i.e., <1 vertebral body length) should undergo attempted thoracoscopic primary end-to-end anastomosis. On the other hand, if there is a "long gap" measuring more than one vertebral body, enteral nutrition is initiated in anticipation that the gap will narrow spontaneously as the two esophageal pouches grow. After 3 months, if the gap has not narrowed sufficiently (i.e., less than one vertebral body) to allow a tension-free DPA, IEE is attempted. However, occasionally patients require an esophagostomy to control secretions, making the proximal pouch unsuitable for IEE. Patients with an esophagostomy and a well-developed distal pouch are ideal candidates EEE (aka Kimura technique). EEE attempts to progressively elongate the proximal esophageal pouch by repeatedly repositioning the esophagostomy. Therefore, it is important to consider EEE as a reconstructive option early so that the esophagostomy can be properly positioned. ER is reserved for patients who require an esophagostomy and have a poor quality distal pouch or in patients in whom esophageal reconstruction has failed. While the best conduit for ER is controversial, laparoscopic gastric transposition is our preferred choice [9].

Delayed Primary Anastomosis

Successful DPA relies on adequate preoperative nutrition and the ability to create a tension-free esophago-esophagostomy. Therefore, we create a gastrostomy as soon as feasible and start enteral feedings early. This plan of care is followed by a variable waiting period of up to 3 months to allow the gap between the pouches to decrease. Continuous suction is applied to the upper pouch and the distance between the upper and lower esophageal segments is assessed periodically with contrast radiographs. If the distal pouch does not fill adequately to assess its length, a metallic dilator can be gently introduced into the esophagus via the gastrostomy using fluoroscopy. The two ends of the esophagus should meet or slightly overlap to ensure a tension-free DPA. In about 75 % of cases, the esophageal gap narrows sufficiently to allow DPA. On the other hand, if after 3 months, a long esophageal gap persists, further waiting is not productive and esophageal lengthening with traction should be considered.

Operative Technique

Three hours before induction of general anesthesia, gastrostomy feedings are stopped, and the upper esophageal pouch is continuously aspirated until the patient arrives in the operating room. The suction catheter in the upper pouch is replaced with a flexible bougie, being careful to keep the bougie separate from the endotracheal tube. While still supine, a radio-opaque semirigid bougie is inserted into the gastrostomy and positioned in the lower esophageal pouch under fluoroscopy. The end of the bougie is positioned such that it can be manipulated though the drapes during the operation. The bougies are indispensable in identifying the ends of the esophageal pouches during the operation [10].

The operation is performed via right thoracoscopy. The patient is placed in left lateral decubitus position and rotated anteriorly into a three-quarter prone position with the right arm reaching toward the head. The surgeon and assistant surgeon stand on the left side of the table facing the monitor located opposite them near the head of the table. The anesthesiologist stands at the head of the table and the scrub nurse at the foot (Fig. 23.3).

In general, special equipment is not needed for thoracoscopic repair of pure EA. While the dissection can be carried out with monopolar electrocautery, a 5 mm LigaSure (Covidien, Mansfield, MA) is useful for ligating the azygos vein. Intraoperative fluoroscopy helps identify

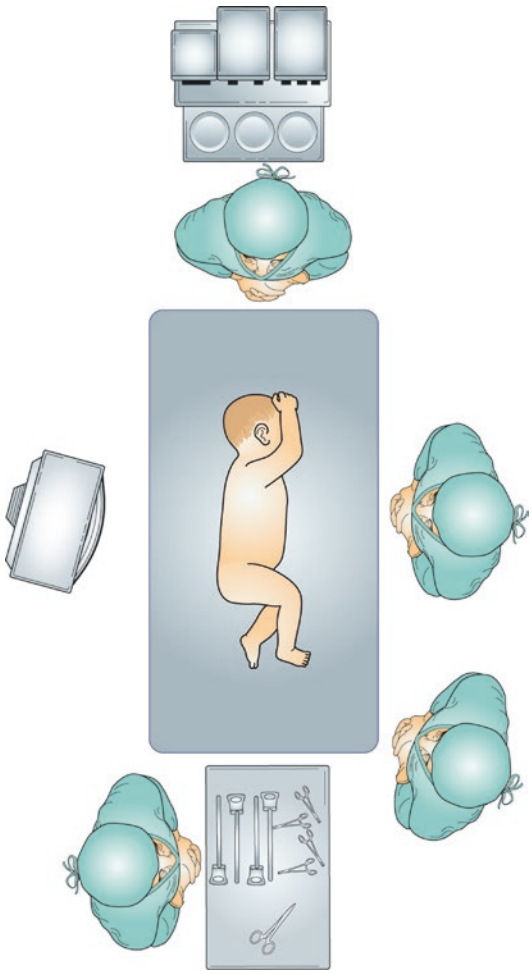

Fig. 23.3 Operating room setup for EA repair. The patient is in the left lateral decubitus position and rotated anteriorly to provide access to the posterior mediastinum

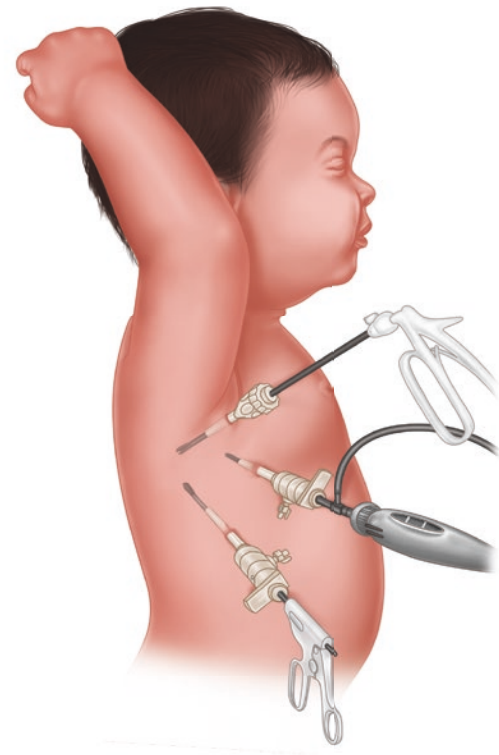

Fig. 23.4 Three ports are routinely used for the dissection and intracorporeal anastomosis: 3 mm camera port in the sixth intercostal space, 5 mm working port in the third intercostal space, and 3 mm working port in the ninth or tenth intercostal space

the esophageal pouches, but is not essential. For the anastomosis, we use 5-0 polydioxanone suture on a CV1 needle.

Three cannulas are positioned as shown in Fig. 23.4. A 3 mm port is inserted in the sixth intercostal space at the midaxillary line and serves as the camera port. We recommend using a short (18 cm) 3 mm telescope with a 30° wide-angle lens because it provides better visibility in the infant's small thoracic cavity. Rather than using single-lung ventilation, CO_2 is insufflated to create a pneumothorax. A pressure of 5 mmHg provides excellent lung collapse without compromising cardiopulmonary physiology. The second cannula is 5 mm and is inserted in the third intercostal space at the midaxillary line. This cannula is larger than the others because it is the primary working port and is used for introducing suture into the thoracic cavity. We recommend using a 3 mm reducer cap to prevent CO_2 leak through the cannula. Finally, a 3 mm port is inserted in ninth or tenth intercostal space at the posterior axillary line. All the cannulas are fixed using the Shah-Neto technique for stabilization which also helps prevent CO_2 subcutaneous emphysema [11].

The first step in DPA is identifying and mobilizing the proximal and distal esophageal pouches. We start by transecting the azygos vein with either monopolar electrocautery or the LigaSure. With the azygos vein divided, we locate the distal esophageal pouch by gently moving the rigid bougie that was inserted through the gastrostomy. The

distal esophageal pouch is dissected from the surrounding tissues by a combination of hook electrocautery, Maryland dissector, and scissors. Great care should be taken with this portion of the dissection as the distal esophageal pouch is thin-walled and easily injured. Next, the proximal esophageal pouch is similarly identified and mobilized. Generally, mobilizing the proximal esophageal pouch off the trachea is the most difficult part of the dissection because it requires dissection up into the neck. The dissection is complete when the proximal and distal pouches slightly overlap with minimal tension. In theory, esophageal mobilization should be limited to what is needed to create a tension-free anastomosis, thereby preserving the segmental blood supply to the esophagus. However, in practice, both esophageal pouches are fully mobilized to reduce tension at the anastomosis.

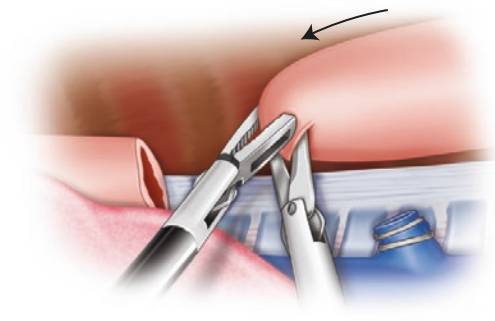

Fig. 23.5 After the proximal and distal pouches are fully mobilized, a transverse esophagotomy is made at the end of the proximal pouch. The distal esophagotomy has already been created

Once the esophageal pouches are adequately mobilized, transverse esophagostomies are made in the ends (Fig. 23.5). Placing tension on the bougies helps identify the very distal part of the esophageal segments and maximizes esophageal length. A primary, single layer end-to-end anastomosis is then performed. The first stitch is placed at the midportion of the posterior wall and knotted in the lumen of the esophagus (Fig. 23.6a). Roeder knots are tied extracorporeally and slid into place using a needle driver, thereby allowing the surgeon approximate the ends of the esophagus despite the tension (Fig. 23.7). Once the posterior wall is approximated, a silastic nasojejunal feeding tube is introduced across the anastomosis to prevent including the posterior wall of the esophagus in the anterior wall closure. As the surgeon transitions to working on the anterior wall of the anastomosis, the knots are tied outside the esophagus. A total of six to eight interrupted stitches are usually needed (Fig. 23.6b). At the end of the operation, an 8–12 Fr. chest tube is left.

We have developed maneuvers to help overcome the technical challenges of thoracoscopic

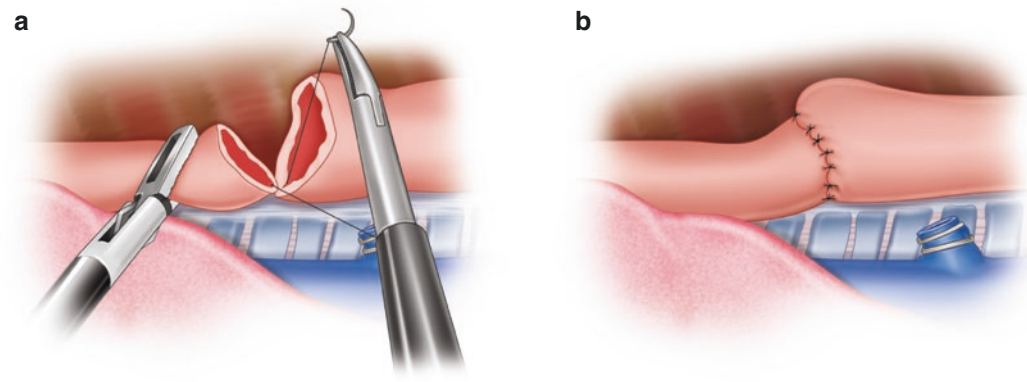

Fig. 23.6 The first stitch is placed in the middle of the posterior wall and the knot is tied on the luminal side of the anastomosis (**a**). The esophago-esophagostomy is complete with six to eight stitches. Note that the knots on the anterior wall are extraluminal (**b**)

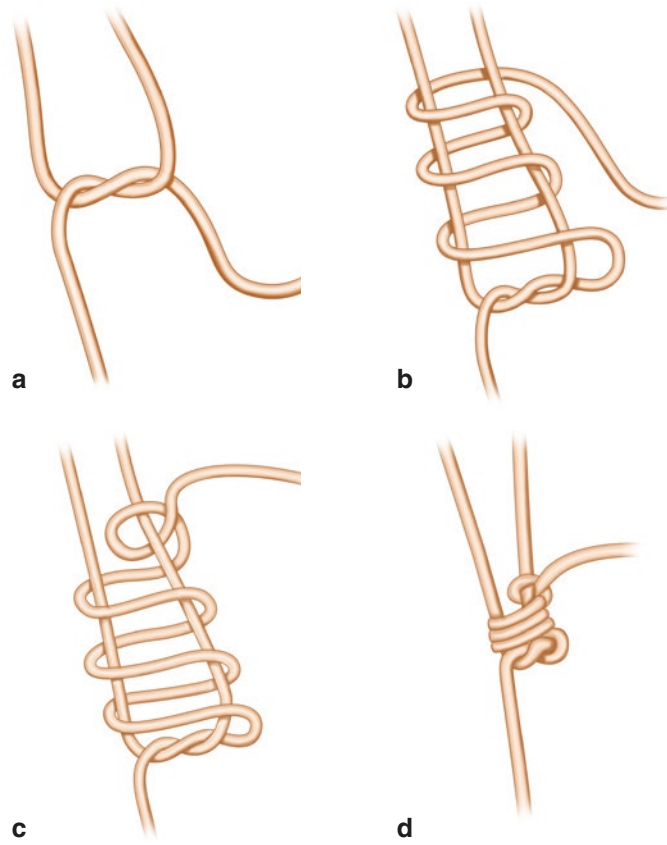

Fig. 23.7 Roeder knots are used because the anastomosis is often under considerable tension. (**a**) A simple knot is tied extracorporally. (**b**) An end of the suture is wound around the suture leading to the knot. (**c**) Next, a half hitch is tied. (**d**) The tension on the knot can be adjusted by pushing the knot down with a needle driver

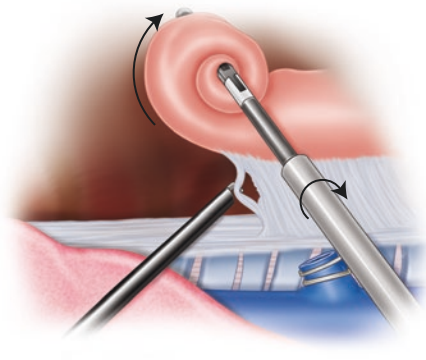

Fig. 23.8 The "spaghetti maneuver" facilitates dissection of the plane between the proximal pouch and the trachea by providing constant tissue traction as the dissection progresses into the neck

repair of EA. As mentioned previously, dissection between the posterior membranous portion of the trachea and the anterior wall of the upper esophagus can be difficult. The "spaghetti maneuver" aids in this portion of the dissection (Fig. 23.8). First, the distal end of the esophageal pouch is mobilized, and the end of the pouch is firmly held with grasping forceps. As the dissection continues proximally, the esophageal pouch is rolled onto the grasping forceps (like spaghetti on a fork) creating constant tissue traction while keeping the mobilized portion of the esophagus out of visualization [6, 7]. In this way, the dissection is continued well into the neck in order to minimize tension at the anastomosis. Because the anastomosis is often under tension despite extensive mobilization of the esophagus, the "twin traction suture" was developed (Fig. 23.9). To distribute the tension evenly, two stitches are placed in the posterior wall of the esophagus and tied simultaneously with Roeder knots. Alternately, tightening the knots gently approximates the tissue and prevents placing all the force on a single stitch [6, 7].

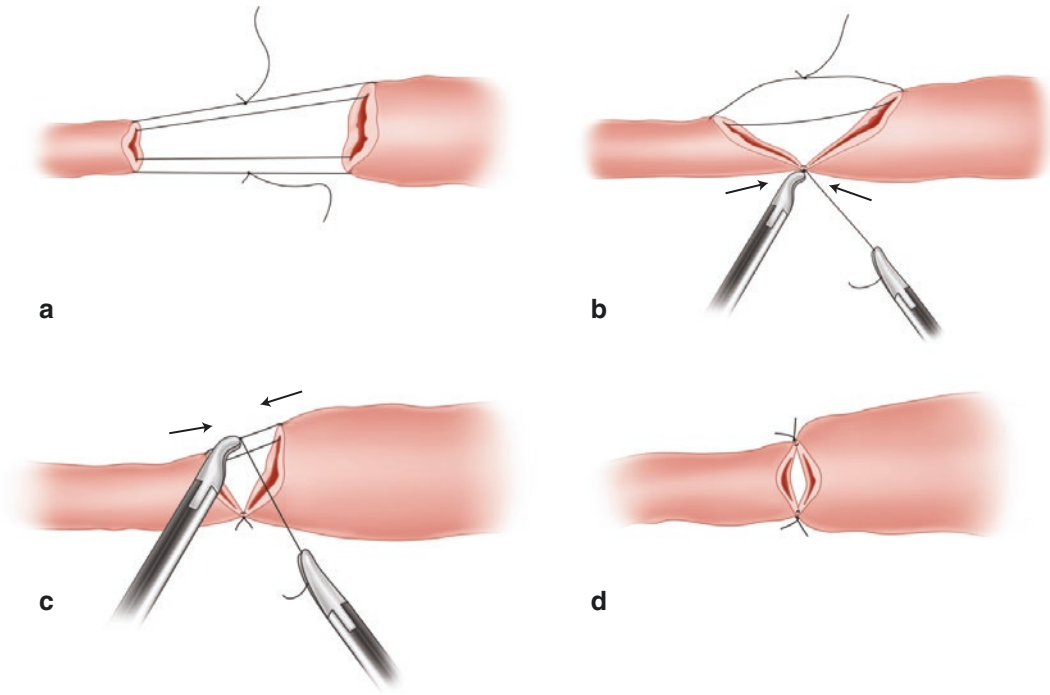

Fig. 23.9 The "twin traction" technique helps approximate the proximal and distal pouches when they are under significant tension (**a**). Two Roeder knots are alternately tightened (**b**–**d**), thus distributing the tensile force and avoiding tears in the esophagus

All patients with high-tension esophageal anastomosis receive full muscle relaxation and are mechanically ventilated for at least 48 h. While muscle relaxation has not been shown to prevent anastomotic problems, we feel it is important to prevent neck extension and excessive swallowing in the early postoperative period. The gastrostomy is vented for 48–72 h and nasojejunal feedings are started on postoperative day 3. A barium esophagogram is performed on postoperative day 5. If the anastomosis is patent and without leak, oral feedings are started and the chest tube is removed. The gastrostomy is left until it is no longer needed.

Intrathoracic Esophageal Elongation (IEE)

IEE is the best alternative for esophageal lengthening if the esophageal gap is greater than one vertebral body height after 3 months of nonoperative management. While various methods for IEE are described, all of the techniques require a relatively well-developed distal pouch and cannot be used in patients with an esophagostomy. In 1971, Rehbein and Schweder were the first to use silver olives as a traction elongation device [12]. An olive is placed in the lumen of each pouch. A nylon suture bridges the esophageal gap and connects the two silver olives. The tension on the nylon suture is adjusted periodically, placing traction on the esophagus and drawing the two ends together. Traction is applied until the two olives are in direct contact and a fistula forms between the two esophageal segments, eliminating the need for an anastomosis. Another group described an innovative thoracoscopic approach to IEE using a magnetic traction device [13].

Our preferred method of IEE is called the "stainless steel spheres technique" (Fig. 23.10) [6, 7]. A stainless steel sphere is placed in both the proximal and distal esophageal pouches. Traction on the two spheres is periodically adjusted by

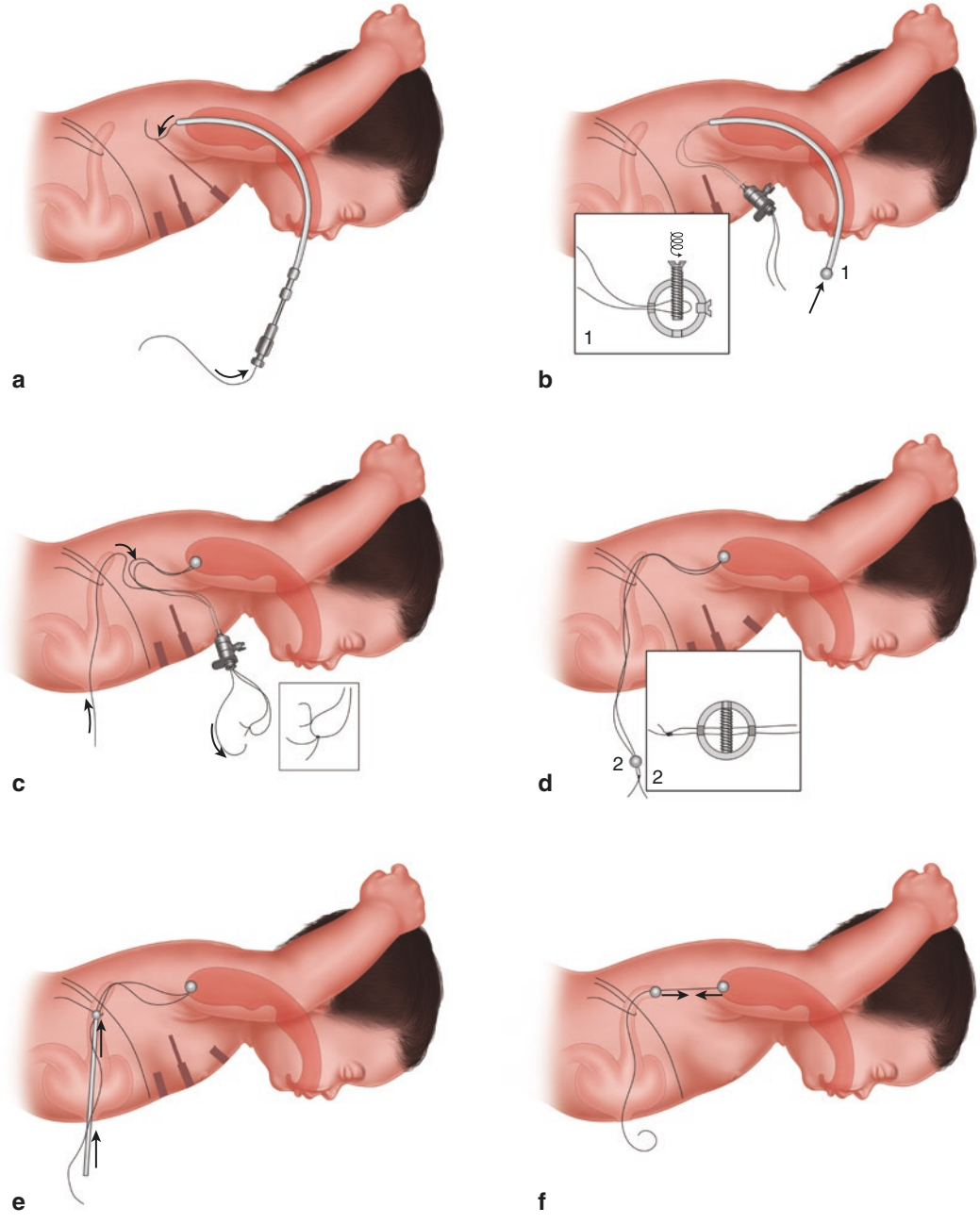

Fig. 23.10 The "stainless steel spheres technique" is depicted. (**a**) A 6-0 Prolene suture is introduced into the thorax and withdrawn from the axillary port. (**b**) The 6-0 Prolene is pulled back and exchanged for a loop of 5-0 Prolene. The 5-0 suture is then attached to a sphere with a removable axis. (**c**) The sphere is pulled into the proximal pouch and a 6-0 Prolene suture is passed through the distal pouch. (**d**) The 6-0 suture pulls the loose ends of the 5-0 suture out the esophagostomy, and the 5-0 suture is attached to the sphere with a fixed axis. (**e**) The 5-0 suture is tied with a Roeder knot and the knot is pushed into the distal pouch. (**f**) The Roeder knot is tightened weekly to maintain traction on the esophagus

tightening the traction suture that is accessed via the gastrostomy stoma. In addition to standard thoracoscopic equipment, IEE requires specialized instruments and devices including the following: two 14 Fr. semirigid, radio-opaque dilators with a hollow central channel, one transurethral injection needle (33 cm long with 23-gauge needle available from Bard, Inc.), one stainless steel traction sphere with a removable axis, and one stainless steel traction sphere with a fixed axis. Intraoperative fluoroscopy is important to ensure proper positioning of the dilators and spheres.

Tube feedings are held 3 h prior to the operation and the patient is placed under general anesthesia. Single-lung ventilation is not required. With the patient supine, a 14 Fr. dilator is passed under fluoroscopy through the gastrostomy and into the distal esophageal pouch. Similarly, a 14 Fr. dilator is passed through the mouth and into the proximal pouch. The dilators are included in the operative field as the surgeon will need access to the dilators during the operation. Next, the proximal and distal esophageal pouches are mobilized thoracoscopically in the same way as for DPA. Special care must be taken to avoid injuring the esophageal pouches because the subsequent repair is at high risk for leaking due to the traction that is placed on the esophageal segments.

Once the esophageal pouches are fully mobilized via thoracoscopy, a traction suture is passed from the upper pouch to the lower pouch. This is accomplished with the transurethral needle and a series of sutures exchanges. First, the transurethral needle is inserted into the hollow channel of the upper dilator and pierces the proximal esophageal pouch. A 6-0 monofilament suture is advanced through the transurethral needle, into the posterior mediastinum, and exteriorized via the axillary port. The proximal dilator and transurethral needle are then removed. The exteriorized end of the 6-0 suture is tied to the middle of the traction suture (5-0 Prolene) and the 6-0 suture is pulled back out of the mouth. In doing so, a loop of the traction suture is brought through the proximal pouch and out the mouth, with the two free ends of the traction suture dangling from the axillary port. The next objective is to pull the two free ends of the traction suture through the distal pouch and out the gastrostomy site. To do this, the transurethral needle is inserted through the dilator that was positioned in the distal esophageal pouch via the gastrostomy stoma. The needle punctures the end of the distal esophageal pouch, and a 6-0 suture is passed through the needle into the mediastinum and exteriorized via the axillary port. The exteriorized 6-0 suture is tied to the two free ends of the traction suture. The 6-0 suture is then pulled back from the gastrostomy site, bringing the free ends of the traction suture through the distal esophageal pouch and out the gastrostomy site. The end result is a single traction suture that forms a loop at the mouth, bridges the esophageal gap, and has two free ends exiting the gastrostomy site.

With the 5-0 traction suture in position, the steel sphere with the removable axis is secured to the loop of suture that exits the mouth. Under fluoroscopy, the surgeon pulls on the free ends of the traction suture, thereby pulling the sphere through the mouth and into the proximal esophageal pouch. Similarly, the ends of the traction suture are threaded through the steel sphere with the fixed axis and pushed through the gastrostomy stoma and into the distal esophageal pouch. The traction suture is tied extracorporally with a Roeder knot and the knot is tightened within the distal esophageal pouch with a knot pusher until there is traction on the esophageal pouches. Note the knot pusher passes over the traction suture, through the gastrostomy site, and into the distal esophageal pouch. A 12 Fr. chest tube is inserted and a chest radiograph is obtained to determine the position of the spheres. Each week, the Roeder knot is tightened through the gastrostomy stoma, using fluoroscopy to gauge the esophageal gap. After 3–4 weeks of traction, the esophageal gap is narrowed, and thoracoscopic DPA is performed.

An alternative to the stainless steel spheres technique is to use sutures to approximate the two ends of the esophagus. The proximal and distal pouches are fully mobilized thoracoscopically as previously described. Next, two or three 5-0 monofilament stitches are placed between the upper and lower pouches and exteriorized out the

axillary port. The stitches are tied with Roeder knots and tightened with a knot pusher. Each week, the patient returns to the operating room and the knots are tightened to increase traction on the esophageal segments. DPA is performed when the esophageal pouches are approximated without tension. The main disadvantages of this technique are: (1) the tensile forces are focused on two or three discrete points, and (2) the patient must undergo general anesthesia each time the knots are tightened.

Extrathoracic Esophageal Elongation (EEE)

The EEE was originally described by Kimura et al. [14] and has proven to be a valid means of esophageal reconstruction when the proximal pouch has been used for esophagostomy or damaged by prior attempts at esophageal reconstruction [15–17]. It is important to remember that, at best, EEE will lengthen the proximal pouch 3–4 cm. Thus, the success of an EEE is predicated on two factors: (1) a good quality distal pouch that at least reaches the level of the carina and (2) not injuring the proximal pouch with each lengthening procedure. While the primary objective of EEE is to preserve the esophagus as the conduit in the chest, an added benefit is that patients can eat while awaiting definitive repair because they have esophagostomies. Though there is no nutritional benefit to eating, these so-called sham feedings are thought to prevent the development of food aversion.

EEE is performed in two stages: (1) esophageal lengthening and (2) establishing esophageal continuity. Esophageal lengthening is achieved by creating a series of esophagostomies that put the proximal pouch under tension, thus progressively elongating the pouch. It is crucial that the surgeon has a clear strategy for executing an EEE when performing the initial esophagostomy; otherwise, the proximal esophageal pouch may be rendered useless. We prefer positioning the esophagostomy on the right side because it simplifies the final operation which requires access to both the esophagostomy and right chest. To create the esophagostomy, an incision is made in the neck just anterior to the right sternocleidomastoid muscle and the dissection is carried down to the esophagus. It may be necessary to transect the anterior scalene muscle to adequately expose the esophagus at this level. Once the esophagus is encircled, the thoracic portion of the proximal pouch is easily mobilized with blunt dissection through the cervical incision. The proximal esophageal pouch is delivered out the neck incision, and a subcutaneous tunnel is made from the neck incision onto the chest. An exit incision is made on the chest, the pouch is passed through the tunnel, and an end esophagostomy is created. The tunnel should be long enough that the esophagostomy is under tension. Two weeks later, the entire proximal pouch is mobilized again, the subcutaneous tunnel is lengthened, and a new esophagostomy is created further down on the chest wall. Counter incisions along the length of the tunnel may be needed to prevent injuring the esophagus during dissection and mobilization. This procedure is repeated every 2 weeks, progressively lengthening the pouch with each esophagostomy (Fig. 23.11).

Once the proximal pouch is of adequate length for a tension-free anastomosis, esophageal continuity is established. The right hemithorax and right arm are fully scrubbed and the arm is wrapped in gauze to allow the patient to be repositioned between the cervical and thoracoscopic portions of the operation. Stay sutures placed at the end of the extrathoracic esophageal pouch serve as a handle for manipulating the esophagus. The pouch is bluntly mobilized from the surrounding soft tissue and may require counter incisions over the neck and chest to avoid injuring the esophagus (Fig. 23.12a). Once the proximal esophageal pouch is mobilized, the distal esophageal pouch is thoracoscopically mobilized as described for DPA. Next, the surgeon bluntly develops a tunnel in the prevertebral space from the right neck into the right thorax. The thoracic portion of the dissection is performed using thoracoscopy. The proximal esophageal pouch is then pulled through the tunnel by the stay sutures using a 3 mm grasper (Fig. 23.12b). The surgeon

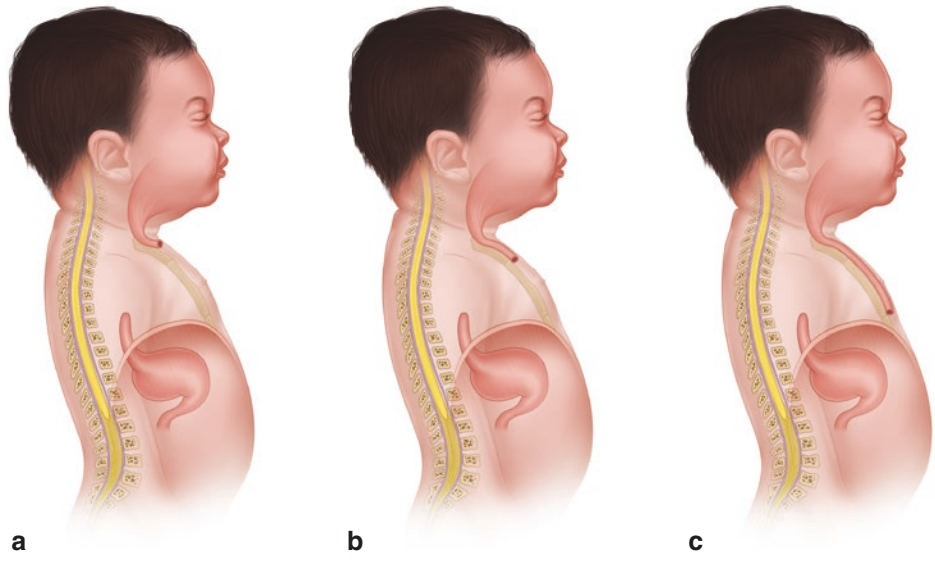

Fig. 23.11 With the extrathoracic esophageal elongation technique, the proximal esophageal pouch is lengthened by serially repositioning the end esophagostomy to maintain traction on the pouch (**a**–**c**)

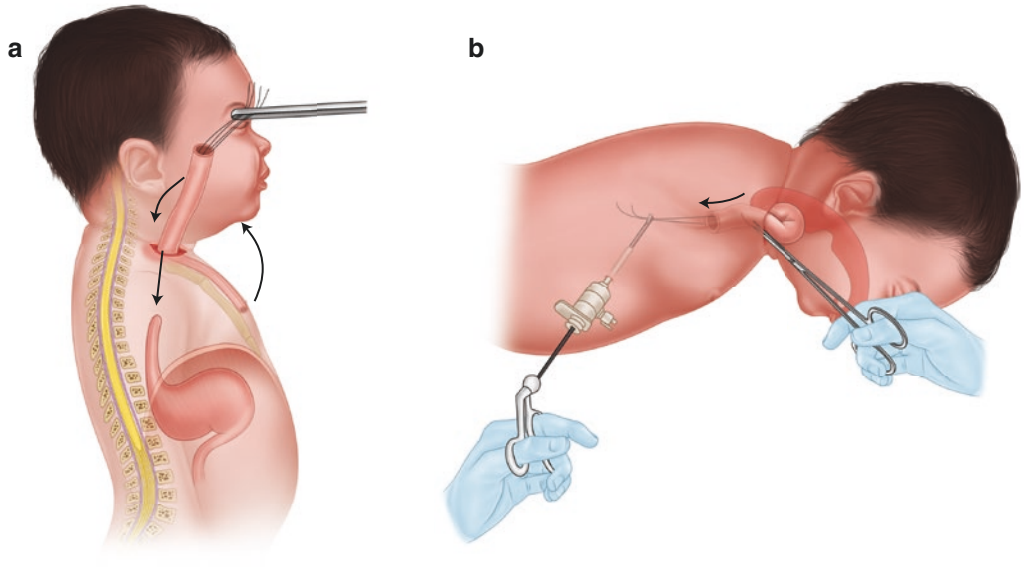

Fig. 23.12 When it is time to establish esophageal continuity, the proximal esophageal pouch is mobilized from the surrounding subcutaneous tissue (**a**). Following mobilization of the pouch, it is pulled through the prevertebral tunnel using the stay sutures (**b**)

must be sure that the esophagus is not twisted as it enters the thorax. Finally, the esophagoesophageal anastomosis is performed using the same technique described for DPA. Postoperative care is similar to DPA patients.

Esophageal Replacement (ER)

Esophageal replacement for EA is reserved for two groups of patients: (1) infants with a poor quality distal pouch requiring esophagostomy and

(2) infants with a damaged esophagus due to failed attempts at establishing esophageal continuity. While there is controversy as to the best conduit for ER, the colon was the first conduit used and remains the most commonly used replacement today. However, we prefer the gastric pull-up as it is technically straightforward and has excellent functional outcomes. Other techniques include gastric tube and jejunal interposition graft. The best reconstructive option for each patient depends on many factors including the length of usable esophagus, length of esophageal gap, and prior operations to the esophagus, stomach, and colon. In general, the shortest, straightest conduit will confer the best functional outcome. While a complete discussion of ER is beyond the scope of this discussion, thoracoscopic and laparoscopic techniques can be used to mobilize the conduit on its vascular pedicle and create the anastomosis. The surgeon must not only consider the optimal type of conduit, but also its preferred location. We prefer placing the conduit in the mediastinum because it offers the shortest, straightest route to the abdomen. However, if there is a thoracic vascular malformation on preoperative CT, the retrosternal position is used.

Conclusion

EA is an uncommon rare congenital defect that is particularly challenging to treat, not only because of the large esophageal gap that must be bridged but also because of the many anatomic factors that influence the strategy for reconstruction. The algorithm detailed in this chapter places patients into distinct treatment groups based on the anatomy and provides the groundwork for thoracoscopic esophageal reconstruction. Using this approach, the esophagus is preserved in 80 % of cases with excellent functional outcome. We advocate making every attempt at reconstructing the esophagus and keeping ER as a second option.

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Part VI

The Growth Procedure for Long Gap EA

24 Growth Induction (the Foker Procedure) and a Flexible Approach for the Repair of Long-Gap Esophageal Atresia

John E. Foker

Introduction

Long-gap esophageal atresia (LG-EA) has posed repair difficulties for surgeons in rough proportion to the gap length. The possibility of repair will also be affected by the size and condition of the patient and the experience of the surgeon, effectively making the gap longer or shorter. As discussed under The Long-Gap Esophageal Atresia Problem (in this chapter), a good working definition of a long gap is whatever distance makes it difficult and risky for the surgeon to try a true primary repair. It is also clear that a gap length declared by some writers to be favorable for a primary repair will not necessarily be satisfactory in other operating rooms. Consequently, a long gap will not be defined here by a given length but will be left as a conclusion to be made by the surgeon. Certainly, the decision to attempt a primary repair in a patient with LG-EA should be carefully made with a good understanding of the operative techniques which will make it possible.

The purpose of this chapter is to present a flexible approach which will accommodate the broad spectrum of LG-EA and allow the desirable goal of a true primary repair to be reached in all patients. Our experience has included a wide range of gap lengths and certainly most or all would be considered long gaps by surgeons (Table 24.1). The gap length is principally determined by the size of the lower esophagus which, as will be seen in this chapter, can range from several centimeters long to a primordium only a few millimeters in length (Fig. 24.1). Currently, when the gap is considered too long for a primary repair, an interposition graft is often used to establish continuity [1–3]. Even the smallest lower segment, however, has a normal potential for development and requires only the growth signal to close the gap [4, 5]. We have shown this signal can be reliably enlisted to induce surprisingly rapid catch-up growth and produce an outwardly normal esophagus. The considerable variation in segment size that will be

Table 24.1 Long-gap distribution

Long (2.6–3.4 cm)		N/17
Ultralong (≥3.5 cm)		70
3.5–4.5 cm	(23)	
4.6–5.9 cm	(27)	
6.0–9.9 cm	(16)	
>10 cm	(4)	
		–
Total		87

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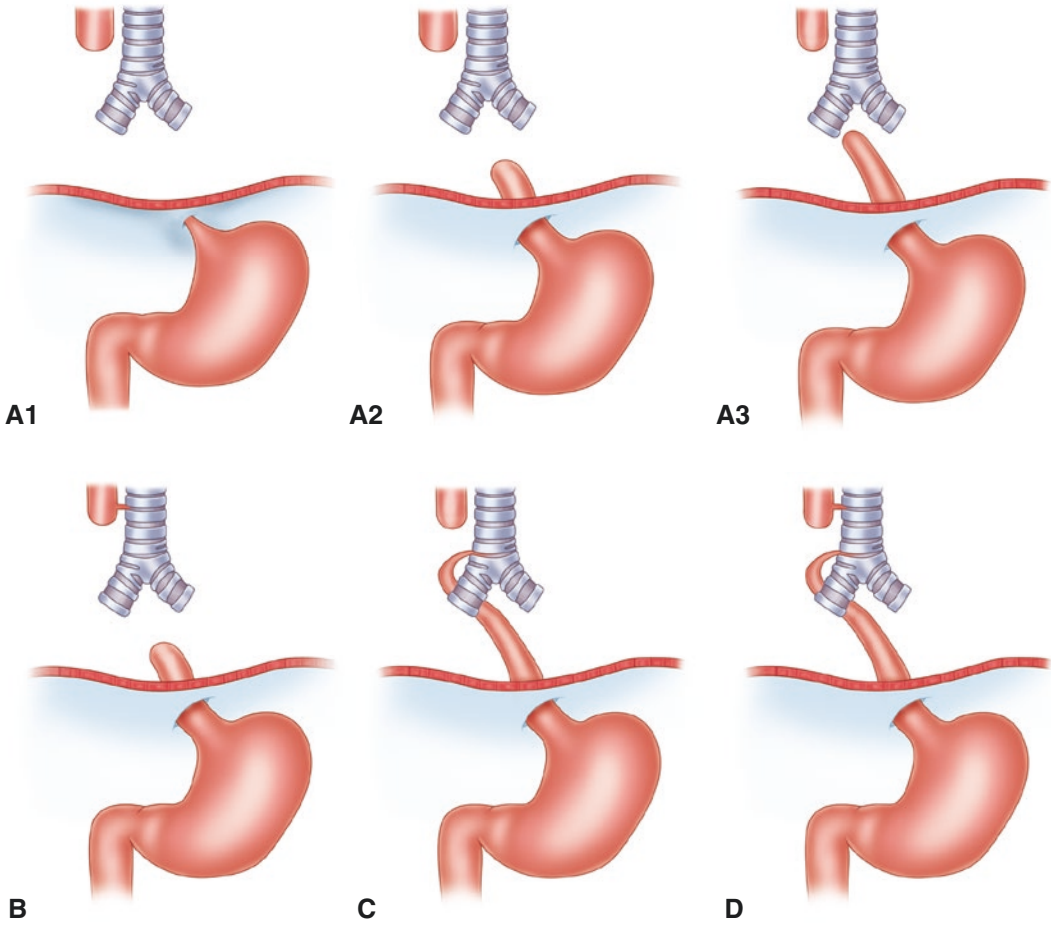


Fig. 24.1 Depicted are the major categories in the esophageal atresia (EA) spectrum. In reality, the spectrum is essentially continuous and intermediate configurations are common. The greatest variation exists in the lower segments. The "pure" EA (type **a**) examples may range from a lower segment not discernible preoperatively ($\mathbf{a}_1$) to one which nearly abuts the upper pouch ($\mathbf{a}_3$). In the group with only an upper pouch fistula (type **b**), a similar range of lower segment lengths presumably occur, but it is a rare type and the variation has not been well documented. There is also variation of where the lower segment enters the airway in types **c** and **d**. The tracheoesophageal fistula (TEF) may enter the membranous septum of the lower trachea or further down in the proximal main stem bronchus (most commonly right for patients with a left aortic arch and left for those with a right arch but other variations occur). These seemingly small differences in distance between the upper pouch and the end of the lower segment can shift an initial primary repair from straightforward to difficult

encountered, however, means the surgical approach must be flexible so that a primary repair can be accomplished across the full LG-EA spectrum [6].

To achieve the desired goal of 70 good years, the anatomy after the repair should be as close to normal as possible. A true primary repair is defined as an esophago-esophageal anastomosis without myotomies or displacement of the GE junction above the diaphragm [4]. In addition to a primary esophageal anastomosis, a good result will also depend on solving the common later problems of reflux and stricture; consequently, our treatment plan for LG-EA patients also includes effective post-repair resolution of these issues. With these problems controlled and despite the lower esophagus having only uncoordinated, sporadic contractions, emptying will be satisfactory with the aid of gravity, and essentially all of the LG-EA children will eat normally.

Our medium-term results support this active approach.

Previous Methods Used to Close a Long Gap

Traditionally, when an LG-EA has precluded a primary repair, numerous different approaches have been tried to achieve continuity, ranging from time to allow the segments to grow to placing an interposition graft. These techniques have had variable early and late results and most are described in other chapters in this book. Certainly, if the lower segment is of moderate size, a period of a few months may allow adequate growth for a primary repair to be done later [7, 8]. A period of relatively rapid induced growth, however, could greatly shorten the time until a primary repair can be done, reducing the intensive care unit stay and leading to earlier eating. Among the other surgical methods to close a long gap, two will be mentioned because of their common usage and significant consequences.

Myotomies, whether circular, multiple, or spiral, divide the muscular layer, allowing the underlying mucosa to stretch and close the gap. Unfortunately, the myotomies also bring their own complications. At the least, myotomies will interrupt coordinated peristaltic activity at that level and hinder emptying down to the anastomotic site. A more severe problem, however, develops when the unsupported esophageal mucosa stretches and forms a diverticulum (Fig. 24.2). Once underway, there is little to prevent an atonic diverticulum from continuing to expand, interfere with the passage of food, and, often, lead to frequent aspiration. With continued enlargement it may even compress the airway creating considerable difficulties in breathing [9, 10]. Consequently, myotomies are not used in our EA repairs.

Another method used by some to bring the esophageal ends together and allow an anastomosis is to open up the hiatus and pull the stomach partway up into the chest. This maneuver also brings very undesirable consequences. With the

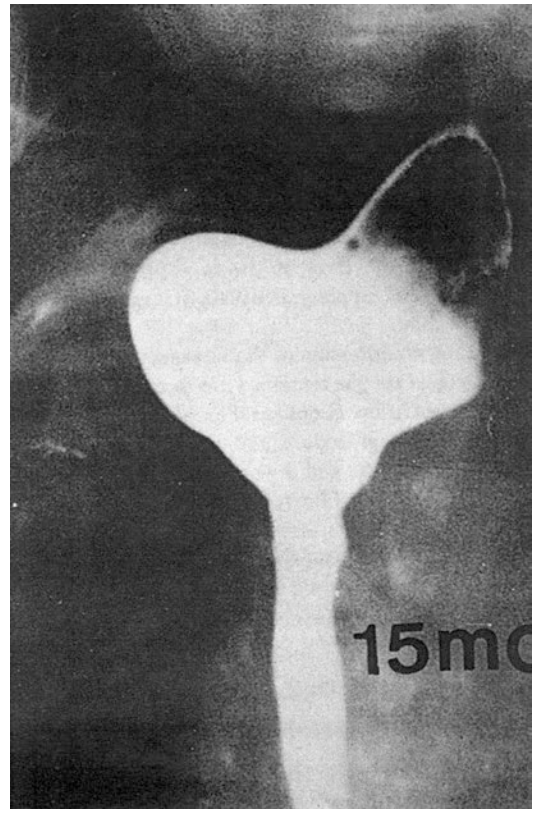


Fig. 24.2 An esophageal contrast study showing a large diverticulum which formed after a circular myotomy. Once a diverticulum begins to form, it tends to slowly enlarge becoming detrimental to swallowing, often resulting in repeated aspiration and may impinge directly on the airway

GE junction subjected to the negative pressure fluctuations within the chest, obligatory reflux up the esophagus will predictably lead to esophagitis and, eventually, Barrett's changes, a precancerous condition. Control of reflux will require establishing a pressure zone at the GE junction. Either the stomach must be returned to the abdomen, allowing a standard fundoplication or, by using a Collis gastroplasty, a type of fundoplication can be created below the diaphragm by wrapping the divided remnant of the greater curvature around the mid-stomach. The Collis gastroplasty, however, would seem to be a poor choice because of the resulting abnormal anatomy which includes leaving gastric cells in the chest and a type of fundoplication which may not function satisfactorily. Even though 20-year and

longer-term data are not yet available for a Collis gastroplasty done in young children, it seems unlikely this configuration will provide 70 good years.

Closing the Gap by Inducing Growth

The Incision and Dissection

The incision has been more completely described. The factors affecting the incision are the side of the aortic arch, the size of the infant, and the length of the gap. Knowing the location of the aortic arch is useful because the repair is better done on the opposite side [11]. Although the esophageal anastomosis can be done on the same side as the aortic arch, it is certainly easier if one does not have to work around the aorta. Furthermore, the presence of LG-EA suggests the possibility of aortic arch anomalies, which may add difficulties to the dissection and repair [12]. It should be remembered that the quality of the anastomosis will be very important to the child and so should be done under the most favorable conditions. Because of the potential consequences of the side of the aortic arch and arch anomalies including the presence of an aberrant subclavian artery, preoperative evaluation of the aorta by echocardiography or a scan will be helpful.

The smaller the lower segment initially, the more likely external traction will be necessary. For the longer gaps reached, there will be a greater advantage, therefore, to having a sturdier baby at least 3–3.5 kg in weight to lessen the possibility the tension sutures will pull out. Briefly, for a 3–5 kg infant, a transverse 3 cm skin incision, beginning just below and posterior to the tip of the scapula and carried back as far as the paraspinal ligaments, will provide an adequate opening (Fig. 24.3). The serratus anterior muscle is spared entirely which avoids later winging of the scapula. The esophagus, even with EA, is located posteriorly and an incision anterior to the tip of the scapula is "empty," and the commonly used large openings will add very little to exposure [13]. For surgeons used to a yawning opening, the incision described may seem limiting at first, but it will quickly become apparent that the exposure is very adequate. The assistant and others will not be able to observe, however, unless a small thorascope is inserted through another interspace. Most, if not all, of the unfortunate sequelae of the traditional, overly generous thoracotomy incision can be avoided with what might be considered a limited opening.

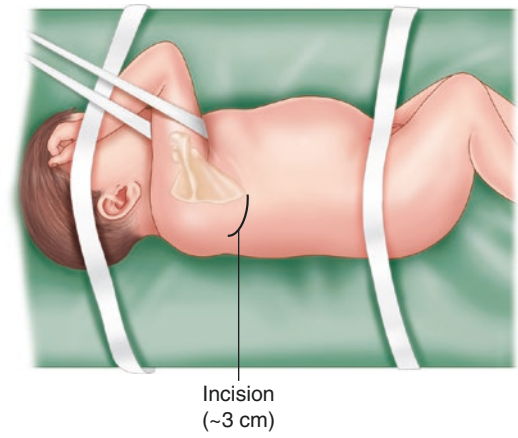


Fig. 24.3 With the patient in a straight lateral position, a 3 cm posterior-lateral incision will be ample for EA repair in newborns. For older children, a 4 cm or slightly longer incision should be adequate. To reduce the sequelae of the thoracotomy incision, the serratus anterior muscle should be spared in its entirety, and, posteriorly, the incision should not divide any perispinal ligaments. To gain access to a high upper pouch, it will be useful go through the third interspace instead of the commonly used fourth or fifth interspaces

Currently, the common type C EA lesions are often repaired thorascopically with equivalent early results to published open procedures [14–16]. One may question, however, whether results from either open or thorascopic procedures which include anastomotic leak rates of 10–20 % and a 5–10 % incidence of recurrent fistulas into the airway are entirely satisfactory. Attempts to improve these results will likely be more successful using open techniques at the present time, although the thorascopic approach will continue to improve as that technology advances.

The applicability of the thoracoscopic approach in LG-EA currently will be largely determined by the size of the lower segment; nevertheless, it has been used in a few cases and centers [17]. In general, the smaller the lower esophageal segment, the greater will be the initial potential problems with growth induction using the thoracoscopic method. The presence of only a primordium would seem to preclude placing traction sutures by this technique into the very small nubbins of esophageal tissue. The thoracoscopic approach has a reduced ability to use the fine sutures and needles which become necessary with very small lower segments. The visibility advantage of the thoracoscopic approach is not great, moreover, because most surgeons use significant magnification during open operations. The choice of how the procedure should be carried out will be better based on the anatomic variables, obstacles, and surgeon experience.

Which intercostal space(s) is opened will depend mainly on the location of the esophageal segments. If the upper and lower pouches are small, the ends may be widely separated and two intercostal openings will be better. The lower segment predictably will often be short if it does not reach the airway and form a fistula (types A and B) although considerable variation is seen (Fig. 24.1). For an upper pouch with a fistula (types B and D), the drainage of saliva into the trachea in utero reduces the growth stimulus of swallowing, and the segment may end relatively high in the neck, contributing to a longer gap. Small segments, whether upper, lower, or both, may be difficult to reach through the standard fifth intercostal opening, so the third and seventh interspaces are often opened instead. The described standard skin incision will allow both of these interspace openings to be made, and carrying them a little further anteriorly underneath the skin will effectively enlarge them and provide satisfactory access to widely separate segments.

A transpleural approach is recommended for any but the most straightforward EA lesions although some centers use it for all [18]. If some degree of growth induction is required, having the esophageal segments within the slippery pleural surface allows the movement of growth. In contrast, if the approach is retro-pleural, the pleural tissues will drape over the esophageal segments, form adhesions, and quickly halt growth. With a well-constructed anastomosis, which will be described in this chapter, there should be essentially no penalty for a transpleural approach [19].

A small lower segment may be difficult to find through a right thoracotomy incision because the esophageal hiatus is usually located on the left side (Fig. 24.4). To locate a small lower segment, a vertical opening is made posteriorly in the mediastinal pleura, the tissues near the vagus nerve are grasped, and with gentle upward traction the dissection proceeds toward the left hemidiaphragm. The undistinguished appearing tissue that is grasped near the vagus nerve contains tissues which envelop lower down, the lower esophageal segment and, sometimes, a small atretic cord from its tip, both of which allow the lower pouch to be pulled upward. With progressive dissection away from the surrounding tissues, the lower esophagus will usually be delivered up into sight, and a suture can be placed in the tip to aid the dissection (Fig. 24.5). Despite the vagueness of this description, this is a very effective technique; after all, the vagus nerves normally pass through the esophageal hiatus on each side of the lower esophagus and should serve as a landmark to begin the search for a very small lower segment.

Additional length in the lower esophagus is developed by taking down all investing tissues as well as limiting small vascular structures. Although the wisdom of dissecting free a small lower pouch has been questioned because of the segmental arterial supply to the normal lower esophagus, the wide experience has demonstrated its safety and confirmed the adequacy of the submucosal blood supply [20, 21]. Occasionally, arterial branches to the esophagus may course superiorly and these may not need to be divided.

The dissection will proceed toward the esophageal hiatus located on the left side of the mediastinum and, often, the left pleura will be visible. Even with a lower segment no more than 2 cm long, with continuing dissection and pulling

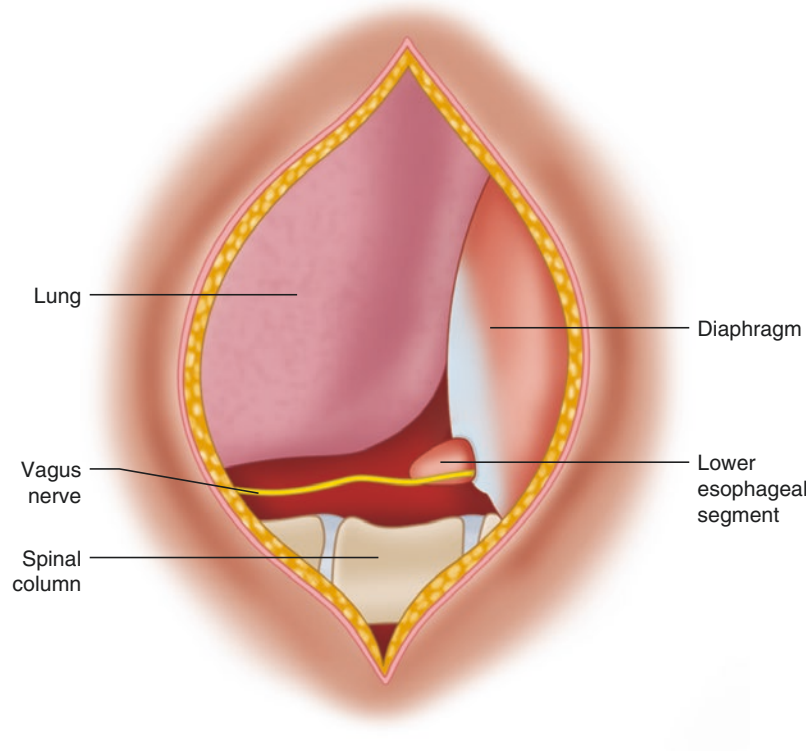


Fig. 24.4 The thoracotomy opening is portrayed overly large in this cartoon and there are no ribs present. If only a very short lower esophageal segment is present, then entrance through the sixth or seventh interspace will put the surgeon just above the diaphragm. The vagus nerve as viewed by the surgeon will be in front of the lower esophageal segment. The mediastinal pleura is opened vertically near the vagus nerve and the deeper tissues are grasped and pulled toward the surgeon. The dissection aims for the diaphragm posteriorly and to the *left* side

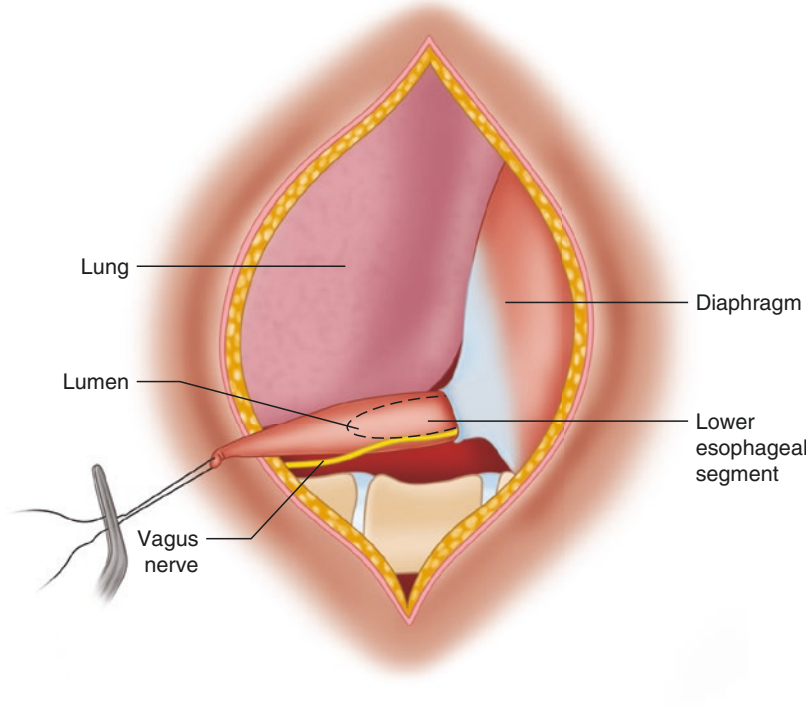


Fig. 24.5 A 5-0 Prolene suture has been doubly placed in the very tip of the lower segment to aid the dissection. This tissue is not strong enough for traction sutures and, more importantly, growth should only be induced at the level which contains a lumen. The vagus nerve is preserved. The dissection should go down to, but not into, the esophageal hiatus leaving the GE junction below the diaphragm

the tissue upward, it will be delivered over to the right side. Although it has been claimed that lower segments that do not appear to end above the diaphragm will be unsuitable for a true primary repair, the results with growth induction have negated this conclusion [22].

An important principle in the dissection of the pouches is to minimize grasping the esophageal ends. Once the segment is located, a 5-0 Prolene suture is doubly passed through the tip, tagged, and used to facilitate the dissection (Fig. 24.5). This technique reduces the need for repeatedly grasping the segment with tissue forceps and damaging the tissues. Cautery is only used on discrete vessels and a bit away from the esophagus.

If the lower esophagus is very small, however, and in effect, only a primordium on the surface of the stomach, an abdominal incision will be required to find it beneath the diaphragm. Inducing growth in a primordium 3–5 mm long is more technically difficult and will take longer, although the end result seems to be equally good. The specific techniques for growing a primordium will be discussed later in this chapter.

For the upper pouch with a suture in the dependent portion, the dissection is carried as high as can be reasonably achieved above the thoracic inlet (Fig. 24.6). The upper pouch may be fused to a variable degree with the membranous portion of the trachea and separation risks entering the airway. The tissue fusing the two structures lacks a defined plane which may make the dissection difficult. The placement of pairs of small vascular clips (Ligaclips®) will compress the fused tissue and allow it to be cut sharply with a #15 blade, reducing the risk of entering the trachea or causing troublesome bleeding (Fig. 24.6). Usually four to five pairs of clips placed successively higher will reach beyond the thoracic inlet and into the neck providing adequate mobility of the upper pouch. The vessels in the fused tissue are not large, and the period of being clamped will control the tendency to bleed even if the clip falls off sometime later.

Occasionally, the upper pouch may require additional freeing up through a cervical incision to achieve adequate mobilization. Mobility is important in realizing the effect of the traction sutures, and a very short upper pouch would be a sufficient reason for a cervical incision. Rarely, unusual or unexpected anatomy might also require cervical mobilization, as in the patient we encountered with a double atresia of the upper pouch. What appeared externally to be an upper pouch of normal length had a lumen which ended higher in the neck. An additional period of traction on the true upper pouch was needed to achieve a primary esophageal anastomosis.

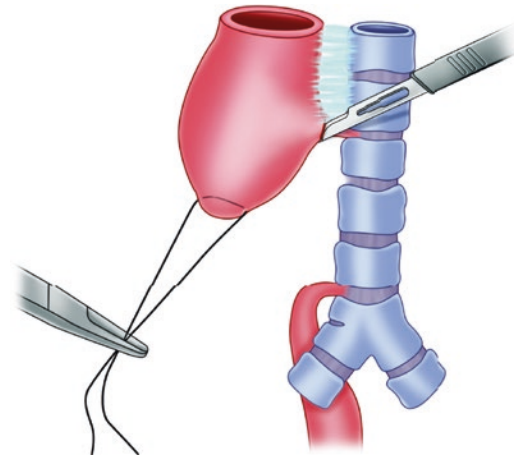


Fig. 24.6 The upper esophagus may be fused to a varying degree with the back (membranous portion) of the trachea. Separating the two structures may be difficult and risk entering the airway or producing bleeding. Clipping the fused tissue with Ligaclips® will help establish the plane between the membranous portion of the airway and the esophagus and allow the compressed tissue to be divided more safely with a #15 blade

For both the upper and lower segments, the dissection is best done by following closely along the esophageal wall. The wall has a characteristic appearance and staying in the plane on its surface is valuable to achieving a neat dissection and avoiding significant vascular structures. An aberrant subclavian artery, for example, would pass posteriorly through the upper chest and has been reported to be a source of bleeding problems during an EA repair. With the more common left aortic arch, an aberrant right subclavian artery would course posteriorly to the esophageal dissection. For a right aortic arch, a left thoracotomy incision might also reveal a left aberrant subclavian artery in a posterior location. Dissecting cleanly along

the wall of the esophageal segments, however, should avoid injuring an aberrant artery and the potential of significant blood loss.

Repair of a Lower Tracheoesophageal Fistula

In some cases of LG-EA, division of a tracheoesophageal fistula(s) may also be necessary. To take down the common configuration of a fistula from the lower esophagus to the trachea or mainstem bronchus, the fistula is first looped relatively near the trachea and dissected free including the neighboring area of the trachea. Once the fistula is well mobilized, it is sharply divided about 2 mm from the contour of the tracheal wall. The resulting cuff provides sufficient tissue for a secure closure without leaving too much behind which would allow a diverticulum to form or so little that closure would be under tension and could somewhat narrow the trachea. Simple interrupted, nonabsorbable 6-0 monofilament (e.g., Prolene) sutures, which have low reactivity and slide through the tissues easily, are placed carefully at the junction with the trachea (Fig. 24.7). These sutures should catch the edge of the membranous trachea surrounding the fistula which will provide greater holding power and a more secure closure.

For a large fistula, where there is concern about a significant air leak after division, sutures can be preplaced near each end before it is divided so the resulting air leak can be promptly controlled sufficiently to allow a careful closure. Because a recurrent TEF (recTEF) is due, at least in part, to microabscesses, using a monofilament suture of low reactivity should help avoid their occurrence.

A vertical closure of the airway defect is easier given the exposure through a posterior-lateral thoracotomy incision and will nicely follow the contour of the trachea. A transverse closure is not necessary and a larger fistula might require pulling the tracheal rings closer together, creating tension. When completed, the tracheal repairs are tested by holding the airway pressure at 40 cm H_2O with the area submerged in saline. Bubbles, of course, indicate a leak and the need for additional sutures. Carefully done, the closed TEF site should be barely discernible looking down the trachea with a bronchoscope.

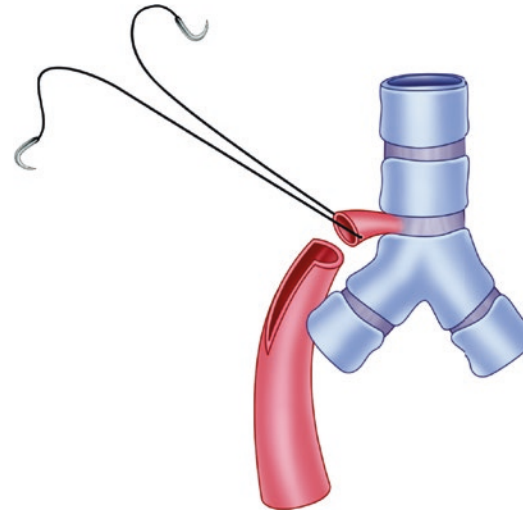


Fig. 24.7 Division of a lower esophageal-tracheal fistula should be done sharply about 2 mm from the junction of the two structures. The closure sutures are placed at the junction, incorporating a very small amount of the membranous septum for strength. A careful closure will neither narrow the trachea nor leave excess tissue which might allow a significant diverticulum to eventually form

Repair of an Upper Pouch Fistula

An upper pouch fistula is usually best approached through a low transverse cervical incision with the neck in extension. The upper pouch is first looped in the neck and retracted upward while the dissection proceeds inferiorly to reveal the fistula. Once divided, the principles of closure will be similar to a lower segment fistula. Closure of the esophageal opening is easily done vertically. The fistulas are relatively small and vertical closure will not compromise the lumen. More importantly, if traction sutures are also needed to induce growth of the upper pouch, the tension will put little distractive force on a vertical closure.

Presence of a Cervical Esophagostomy (Spit Fistula)

Often LG-EA patients have a cervical "spit" fistula created early in infancy to allow passage of saliva until continuity is established. If the decision is made later for a true primary esophageal repair, then growth induction of the upper pouch by one of two methods is desirable to allow the anastomosis to be done in the chest. The first method is to mobilize the upper pouch, securely close the esophagostomy site, and bring it down as far as possible alongside the spinal column. Blunt dissection will easily create a space for the upper esophagus alongside the vertebral bodies. Two pledgeted horizontal mattress sutures are placed in the upper esophagus proximal to the closure line and then into the fascia overlying the vertebral bodies down in the upper chest. By tying the sutures, the closed upper pouch is pulled down into the upper mediastinum, and this amount of tension should not compromise the closure. About 3–4 weeks are required for adequate healing before the upper pouch can be placed on external traction to induce further growth. Obviously, closure recreates the problems of esophageal atresia; however, it is surprisingly well tolerated in infants who easily accommodate to the required intermittent suctioning of saliva.

For patients 2 years of age or older, however, closure with the inability to swallow saliva may not be so well tolerated. In this case, the Kimura downward advancement technique for the spit fistula can be used at 2–3-week intervals [23]. This technique successively lowers the exit site on the anterior chest wall typically gaining about 2 cm on the skin surface and somewhat less in useful length. It is, therefore, a more laborious method which leaves several scars and is advantageous only when the patient will not tolerate the closure method.

In the Minnesota experience, both right ($n=11$) and left ($n=5$) spit fistulas were closed, allowed to heal, and, subsequently, put on external traction. After closure and healing of a left spit, the upper esophagus had to be brought under the trachea and down into the right pleural space so that the traction sutures could be placed and brought out the chest wall posteriorly. Although this was a larger undertaking, it was done successfully in all cases and a true primary esophageal repair was the end result. A recent attempt at closure of a left spit fistula in Boston in a Down patient who was an active air swallower, however, was unsuccessful because the force generated by the swallowed air produced repetitive air leaks into the mediastinum. This combination of congenital problems may be more difficult, making a spit fistula advancement technique the better choice.

The Flexible Approach: Evaluation and Choice of Growth Method

The best time to determine how to proceed with a long-gap EA lesion is in the operating room after both esophageal segments are dissected free and mobilized but before the ends are opened. The sutures in the end of the segments which aided dissection are crossed, and, with a moderate pull, an assessment of the effective gap length can be made.

The gap assessment will be important to choosing which technique to use for growth induction. The choices range from an anastomosis, to the one-time stimulus of internal traction, and to the external tension techniques which provide a repetitive signal and induce more growth. A general classification of the surgical approaches based on apparent gap length has been presented to aid in the decision between an anastomosis or a period of growth (Table 24.2). The specific approach chosen will depend on the surgeon's assessment and, therefore, numerical gap lengths are not given. In general, if there is doubt on which approach to use, the next lower technique in Table 24.2 will produce greater growth and make the eventual anastomosis easier and less risky. For example, external tension will be able to induce greater growth and close a longer gap than the one-time stimulus of internal traction.

Anastomosis

If the ends overlap during the assessment, an anastomosis should be possible. The main additional question will be where the lumens end, and a tube placed into the segments from above and below through the G-tube site will locate them. If the lumens are essentially touching, the ends can be opened, even though some retraction will be likely, and the resulting gap may be longer than anticipated. The anastomosis, nevertheless, should be able to be carried out successfully even if a period of traction in the operating room is needed. This useful technique will be described subsequently in this chapter under section "Growth Induction: The Anastomosis".

Internal Traction

For longer gaps where only minimal overlap of the ends is achieved despite moderate tension on the crossed dissecting sutures, a period of internal traction will make the anastomosis easier and safer. Traction sutures are placed into the esophageal segments in a similar fashion whether they are intended for internal or external traction. The internal traction sutures are anchored into the prevertebral fascia and when tied down will put tension on the segment.

Under more exceptional circumstances, up to three rows of traction sutures have been placed to maximize growth. Particular care must be taken with the middle rows so no significant wall damage occurs.

External Traction

The growth induced by the one-time stimulus of internal traction will be complete, after 5–7 days; nevertheless, it can be significant and make the difficult anastomosis much easier. The amount of growth-inducing tension created by the internal traction will depend on several variables mainly related to suture placement, and, if there is a question on its suitability, it will probably be better to use external traction.

For even longer gaps, when the ends remain apart despite firm pulling on the dissection sutures or when the gap is so long that an attempt to bring the segments together does not make sense, then significant growth by 2 or more weeks of external traction will be required (Table 24.2). The placement and configuration of the traction sutures will be discussed in detail in the next section.

Table 24.2 Flexible solutions for the long-gap problem

Moderate gap:	Traction in OR	(~10 min)
Longer gap:	Internal traction	(5–6 days)
Very long gap:	External traction	(7–21 days)
No apparent esophagus:		
	Grow primordium	(3+ weeks)

Fit the operation to the baby

For some cases with an upper or lower fistula, a period of growth may also be needed to achieve a successful anastomosis. Closure of the fistula site and placement of the two ends on either internal or external traction can be used to stimulate the necessary growth. Occasionally, even the common form (type C) may be judged to have a gap too long for a safe initial primary repair (Fig. 24.1). In that case, it would be better to securely close the fistula and place the two esophageal segments on internal traction for 5–7 days and avoid the problems of a failed anastomosis. This flexible approach should allow a successful true primary repair in virtually all type C lesions.

In the case of an upper fistula (type B), both the upper and lower segments may be short and require external traction to induce sufficient growth for an anastomosis. For the upper pouch, the fistula closure will be vertical and the traction sutures should be placed to avoid the site and not put direct stress on it. Typically, the closed fistula will be near the end of the upper pouch, and the traction sutures can be placed above and away from the closure site. The length of lower segment will be the most variable component and similar to the range found in type A lesions; consequently, in many cases external traction will be necessary to induce sufficient growth for a well-constructed anastomosis.

For all of these techniques, when adequate growth has been achieved, the esophageal ends will retract when released from traction and if finding and opening the lumen also proves difficult, the anastomosis may need to be created under some tension. Consequently, the creation

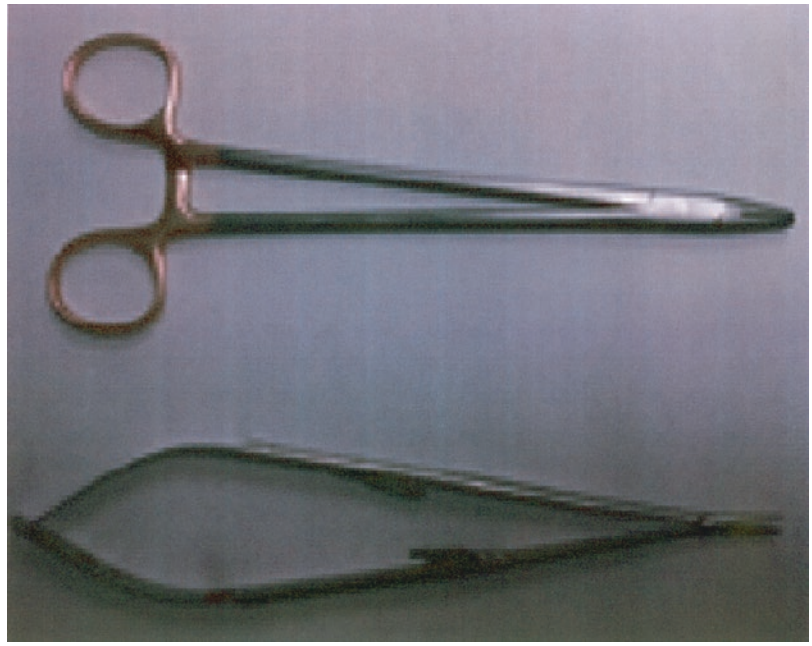


Fig. 24.8 The two basic types of needle holders are pictured. Use of the upper, standard needle holder relies primarily on wrist action although guided by the forefinger. The lower, Castro-Viejo-type needle holder depends mainly on finger motion and provides more feel in the placement of fine needles into delicate tissues

of a well-constructed and reliable anastomosis becomes an important part of the overall growth induction process. The technique of creating a successful repair even under moderate tension will be described in detail subsequently in this chapter (section "Growth Induction: The Anastomosis").

Growth Induction: The Traction Sutures

The traction sutures provide the growth-inducing tension, and their placement will be increasingly difficult, the smaller the esophageal segment. The lower segments may be very small and composed of tissue that is not sturdy, leading to a tendency for the sutures to pull out if too superficially placed. Placed too deeply, however, the sutures will enter the lumen producing a leak and predictable problems. The difficulty in judging the location of the lumen makes suture placement inherently imprecise; nevertheless, good technique and concentration can minimize the problems.

The needle holder and type of suture are of importance. A Castro-Viejo-type needle driver provides the best feel for accurate placement because it is a finger instrument, while the standard needle holder depends more on wrist motion (Fig. 24.8). By using the finger tips for touch and concentrating on the needle placement, a good amount of tissue can be scooped up while still avoiding the lumen. In the smaller segments, the stitches will be relatively longer but less deep. A feel for the amount of tissue incorporated will develop with experience, and the Castro-Viejo needle holder will likely be used for virtually all suturing.

To place a traction suture, the needle enters at a right angle to the surface at a point where the lumen is judged to begin. If the traction sutures are placed at the very end of the segment, much of the growth will be induced in the solid end and without a lumen. The depth is by feel and when the muscular layer seems to have been included, the needle should be turned to avoid the mucosa. A relatively long tissue bite is taken for strength (Fig. 24.9a). These are important sutures and the surgeon should concentrate on the placement.

For traction sutures, we have used a monofilament, nonabsorbable suture such as polypropylene (Prolene) because it is smooth and nonreactive. For the larger suture sizes (e.g., 4-0), a small needle is not readily available; consequently, for infants with LG-EA, a 5-0 suture is

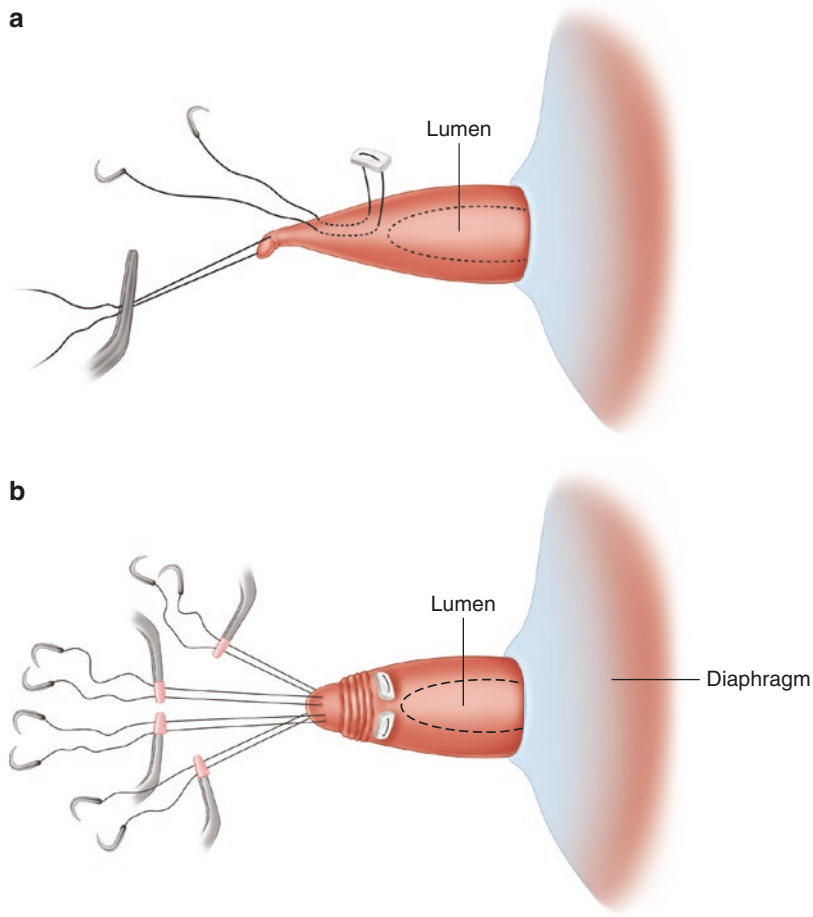


Fig. 24.9 (**a**) This figure portrays the placement of the pledgeted traction sutures. A pledgeted 5-0 Prolene in infants or, perhaps, a 4-0 Prolene in older babies seems to be the best choice for size. Prolene moves easily within the pleural space and through the chest wall tissues. The tissue bites are begun where the lumen is thought to end and should be generous to provide holding power but should not be too deep to avoid the lumen and a leak. The "touch" necessary to place theses sutures is better with Castro-Viejo needle holders. If one places the horizontal mattress stitch where the opening of the lower segment will presumably be made, then no usable length will be lost. (**b**) Four traction sutures, the usual number, are shown placed in the lower segment. In the very small lower segments, only two or three sutures can be placed. The configuration of the upper pouch traction sutures will look very similar

commonly used. The 5-0 monofilament suture, however, will stretch on traction and usually requires periodic retying to reduce its length and the number of pieces of tubing needed under each loop to provide tension. For the tiny (primordial) lower segments, a 6-0 or even a 7-0 suture may be used initially to provide internal traction and stimulate growth until the segment is large enough for 5-0 traction sutures.

The holding power is increased by using pledgeted, horizontal mattress sutures and, usually, four are placed (Fig. 24.9b). The pledgets can be cut from packaged material such as bovine pericardium or harvested from the patient's fascia or pericardium. Woven Teflon or Dacron pledgets, in contrast, encourage ingrowth of tissue and will be more difficult to remove at the time of the anastomosis. After the horizontal mattress sutures are

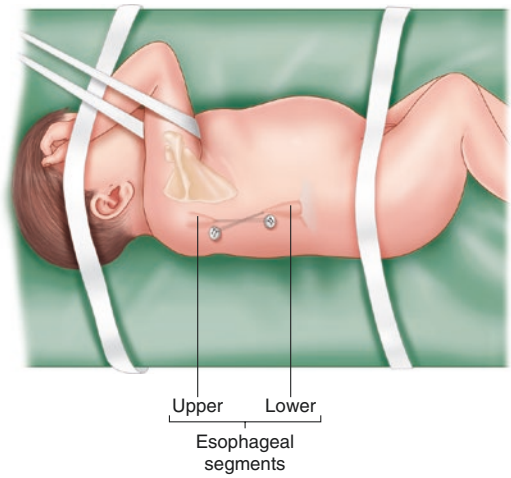


Fig. 24.10 The traction sutures are brought out posteriorly on the chest wall and threaded through a thick silastic button cut for the purpose. There will be significant force exerted by the traction sutures and a broad platform on the skin is useful to prevent the sutures from pulling through. The lower segment sutures are brought out above the incision and the upper pouch sutures below. This allows the segments to cross with growth which will facilitate the primary esophageal anastomosis. Small pieces of silastic tubing are placed underneath the tied sutures on a daily- or twice-daily basis to reestablish the tension lost by segment growth

placed, pulling on them will indicate if the placement and apparent holding power are satisfactory.

The upper pouch sutures are brought out to the skin surface posteriorly and below the incision, while the lower segment sutures exit above it (Fig. 24.10). Bringing out the suture pairs in a square pattern allows them to be placed in a relatively straight line from the esophageal segment to the skin. A piece of very thick silastic sheeting cut into a button shape with four holes cut out in a square configuration will allow the sutures to be brought through the skin in the same pattern as on the esophageal segment. The sutures are tied snugly and the tension increased daily by placing short pieces of silastic tubing under the loops. The lengths of silastic tubing (about 2–3 mm diameter) can be cut from a roll and are economical. It seems likely from basic cellular studies that intermittent increases in tension will produce greater growth than a continuous signal [24].

Alternative methods are certainly possible and in one report, crimpable beads on the traction sutures were used to produce tension with success [25]. Mechanical methods to maintain tension are being developed and one may emerge as an improvement [26]. Whatever method is used to increase the traction tension, one should avoid clamping the sutures which might fracture them and require replacement. A curved mosquito clamp placed under the loop and lifted will provide space for additional pieces of tubing to be inserted.

The button serves as a platform which keeps the sutures from pulling through and spreads the pressure on the skin surface although some skin necrosis often occurs beneath the button. The placement of a padded dressing material (e.g., Telfa) under the button may be helpful in reducing the pressure effects. After the button is removed, the site will heal, although it may leave a small, dimpled scar.

Metal clips placed superficially on the esophageal segments where the lumen is judged to begin allow the growth to be followed by X-ray. When the clips are at the same level or overlapping, the length should be sufficient for an anastomosis even though the segments will retract somewhat when released (Fig. 24.11a, b).

The traction sutures may pull out because of the weak tissue strength of the small esophageal segments (Table 24.3). If one or even two sutures pull free, it may not be significant; however, if more pull out, they may need to be replaced or the anastomosis carried out. Leaks caused by the sutures will be more detrimental although using the technique described, they did not occur during the Minnesota experience. If they occur, however, even with adequate drainage, difficulties may arise and the holes should be closed if more traction is needed.

Certainly, the described traction technique is imprecise and somewhat ornate. It seems very likely that better methods will be developed; nevertheless, the biological principle of tension-induced growth will remain and be utilized for the best results. In the Minnesota series of LG-EA infants without a previous attempt at repair, the initial gap length ranged from 3.1 to 10.6 cm; nevertheless, in all cases sufficient

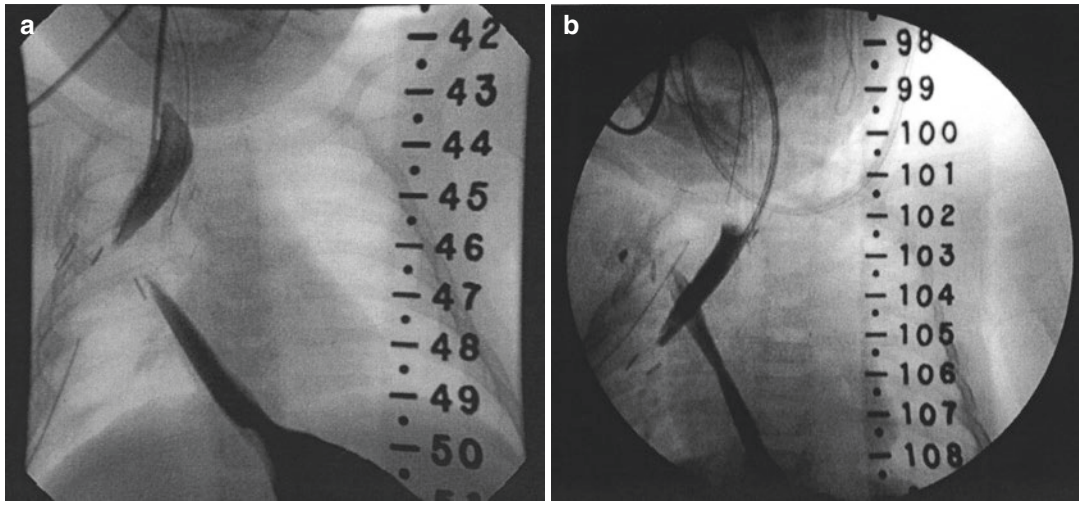


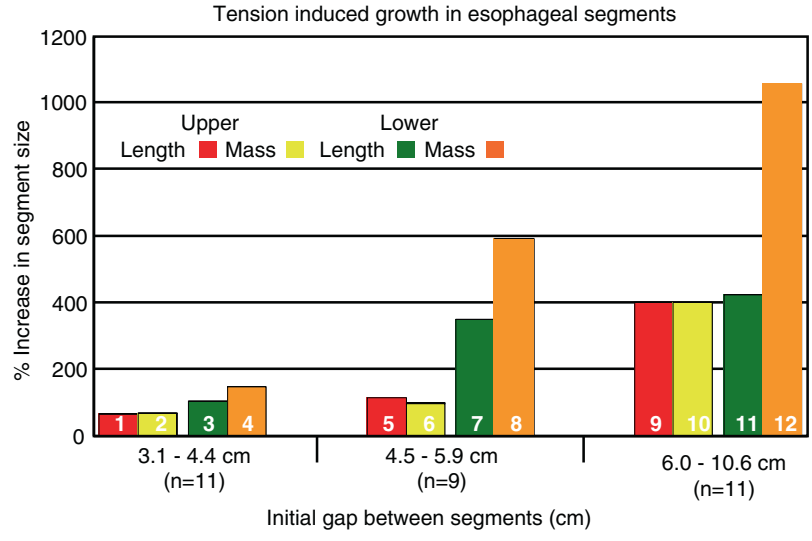
Fig. 24.11 (**a**) A contrast study reveals satisfactory growth and almost enough length for a reasonable primary repair. (**b**) A study shows the segments on traction now overlap and will have suitable length for an anastomosis

Table 24.3 Complications during growth induction

Traction sutures avulsed/replaced	6
Traction sutures reconfigured	8
Esophageal ends freed up	1
Erosion of chest tube into esophagus	1

None prevented primary repair

Table 24.4 Tension-induced growth in esophageal segments



growth was induced for a primary repair (Table 24.4). In two patients, age 2 and 4 with previous attempts at repair, the measured gaps upon arrival at Minnesota were 12.5 and 16.5 cm, and in these too, growth was successful. Growth was successfully induced in an 8-year-old boy with a long hypertrophic fibromuscular stricture indicating the response remains active well into childhood. Growth induction in our experience has always been effective, making a true primary repair possible across the entire EA spectrum.

Growth Induction: The Primordial Lower Esophagus

At the furthest and most difficult end of the esophageal atresia (EA) spectrum are those very uncommon cases in which the lower esophagus is so small that it does not reach the diaphragm. Previously, it was concluded that in these cases, a true primary esophageal repair with the GE junction remaining in the abdomen was not possible [22]. The ability to reliably grow even the smallest primordial nubbins, however, has changed this outlook (Fig. 24.12a–c). In the case illustrated, approximately a 50-fold growth response was necessary to close the gap (Tables 24.5 and 24.6).

These extreme cases have included lower segments whose luminal length was 4 mm or less, and in some, the lumen could not be found preoperatively either by contrast study or endoscopy (Figs. 24.13a, b). Nevertheless, at laparotomy, a lower segment 3–4 mm in length and 2 mm in width was found coming off the stomach at the usual esophageal location high on the lesser curvature. In essence, these nubbins were a primordium, but despite the small size, all the developmental information was present and within 3 weeks a lumen could be seen (Fig. 24.13c). Further growth resulted in an outwardly normal and full size lower esophagus suitable for a primary esophageal anastomosis (Fig. 24.13d). This and other remarkable cases raise the question of whether or not a lower esophagus is ever truly absent.

For the tiny primordium, a 50-fold or greater growth response may be required to turn it into an adequate lower esophageal segment (Table 24.4). The technical details become more important the smaller the segment and will be described in detail. Growing a 3–4 mm lower segment will require time, and it should also be expected that reconfiguration of the traction sutures will be needed on several occasions to maintain the growth-inducing tension.

The surgical steps to grow a primordium must be precisely done. To start growth, two 7-0 Prolene horizontal mattress sutures are carefully placed in the nubbin and fixed only internally to the neighboring fascia to provide tension. The amount of tension should not be too great; the sutures must both hold and stimulate growth. Although internal traction provides only a single episode of tension, it will convert the primordium into a more workable lower segment, perhaps tripled in length and width. Despite the small initial size, the response has been surprisingly vigorous.

As expected, the traction sutures needed to be reconfigured in 5–7 days to maintain the growth signal. The tissue sutures themselves, however, should not be replaced unless necessary in order to minimize trauma to the primordial nubbin and preserve its potential for development. The traction sutures can be tied as a loop over another, heavier, suture such as 4-0 Prolene which can then be anchored and, later, re-anchored into the fascia or the undersurface of the diaphragm to increase tension. Although growth is relatively rapid, it may be 3–5 weeks before the developing lower esophageal segment will be large enough to be brought into the right chest where the more continuous signal provided by external traction can be applied.

Once the length of lower esophagus is sufficient, it is completely mobilized in the abdomen and a pathway into the right chest is created. The normal position of the liver will interfere with this route; therefore, the ligaments of the left lobe are taken down and reattached anteriorly and to the right, moving the liver forward and allowing passage of the lower segment through the diaphragm. The segment will be brought through the right hemidiaphragm rather than a site near a normal esophageal hiatus on the left hemidiaphragm.

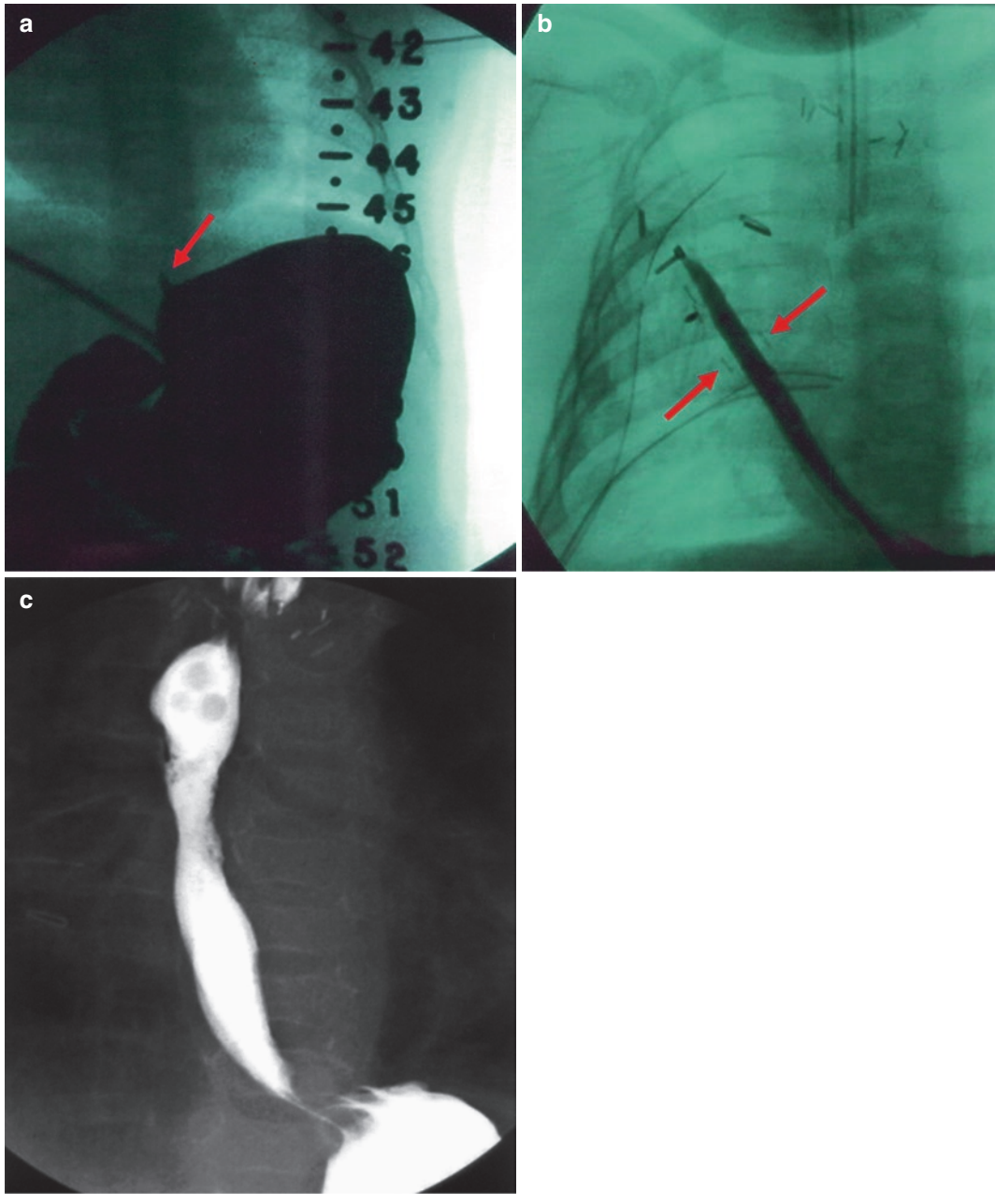


Fig. 24.12 (**a**) A contrast study showed a tiny lower esophageal segment. Two sutures were placed to provide the initial growth stimulus. Subsequently, the sutures were reconfigured and augmented by others. (**b**) In under 3 weeks' time, the lower segment made remarkable growth in both length and also in width as indicated by the *arrows*. (**c**) A contrast study following a primary anastomosis and later fundoplication shows an outwardly normal-appearing esophageal segment with the anastomosis in the usual place

Table 24.5 Growth response (for one patient)

Growth within 12 days:
Lower segment
Length: 3–42 mm (14-fold)
Width: 4–14 mm (3.5-fold)
Total mass (est.): 50-fold increase
Therefore, significant growth, not stretch

Table 24.6 Learning to eat after growth induction LG-EA repair

	LG-EA ($N=21$) months	Normals ($N=26$) months
Finger feeding	15 ± 2 (12)	11 ± 2 (5)
Solids with spoon	22 ± 2 (14)	20 ± 2 (8)
Drinking from cup	21 ± 2 (15)	19 ± 2 (8)
All milestones	26 ± 2 (9)	28 ± 2 (8)

To create the hiatus as well as reconfigure the traction sutures of the lower segment in the right chest, a simultaneous right thoracotomy and laparotomy will be useful. A convenient spot is selected in the right hemidiaphragm relatively near the pericardium. The lower esophagus will pass under the pericardium and anterior of the inferior vena cava leaving only the phrenic nerve as a structure at risk. This nerve, however, is easily identified through the right chest as it courses down the pericardium. The neo-hiatus should be large enough for the lower segment to pass through and accommodate some increase in width but not so large as to admit the upper portion of the stomach.

With the lower segment through the diaphragm, the traction sutures are brought out the chest wall more laterally than superiorly because the segment will be relatively short. More esophageal length will be necessary before it is able to turn superiorly to continue growth; therefore, at least one more reconfiguration of the traction sutures will be required. As before, if the tissue sutures are still well positioned in the esophagus, additional length can be gained by tying the traction sutures over yet another 4-0 Prolene suture. After further growth, the lower esophagus should have a relatively normal intrathoracic course, and a satisfactory anastomosis with the upper esophageal segment will eventually be possible.

As an aide to the growth process and making easier the repeat thoracotomies, the placement of pieces of very thin silastic sheeting around the segment to allow the movement of growth and others to maintain a space between the ribs on closure will be helpful.

When only a tiny lower segment is present, the question of what should be done is certainly relevant. With such a small starting point, should an attempt be made to induce growth? Because of what we believe are the superior long-term results with a repair using one's own esophagus, our answer would be yes. An important caveat, however, would be that attempting to accomplish the needed amount of induced growth should not be undertaken lightly nor without previous experience with this approach. This situation underscores the desirability of having a few centers of substantial competence for the very difficult cases [2].

Growth Induction: Tension and Growth

The ability of axial tension to induce esophageal growth has been well established in numerous human patients. It is also clear that true growth in both length and thickness of the esophageal segments is induced, and these increases are not a product of stretching (Table 24.4). All the necessary information for normal development is contained in the smallest lower segments, and follow-up assessment reveals a normal-appearing wall structure [27, 28].

The details of the amount and timing of tension increases, however, have not been systematically studied. It seems likely that the greatest response will occur with moderate tension, and further increases in force may become ineffective or even detrimental: but this question has not been studied. The amount of tension is clearly limited by the esophageal tissue strength and the holding power of the traction sutures. The lower segment varies most in size and strength, while the upper segment, even with a fistula, will be relatively thick walled from the action of saliva in utero. The variation in reflux in utero means the lower segment may remain only a diminutive

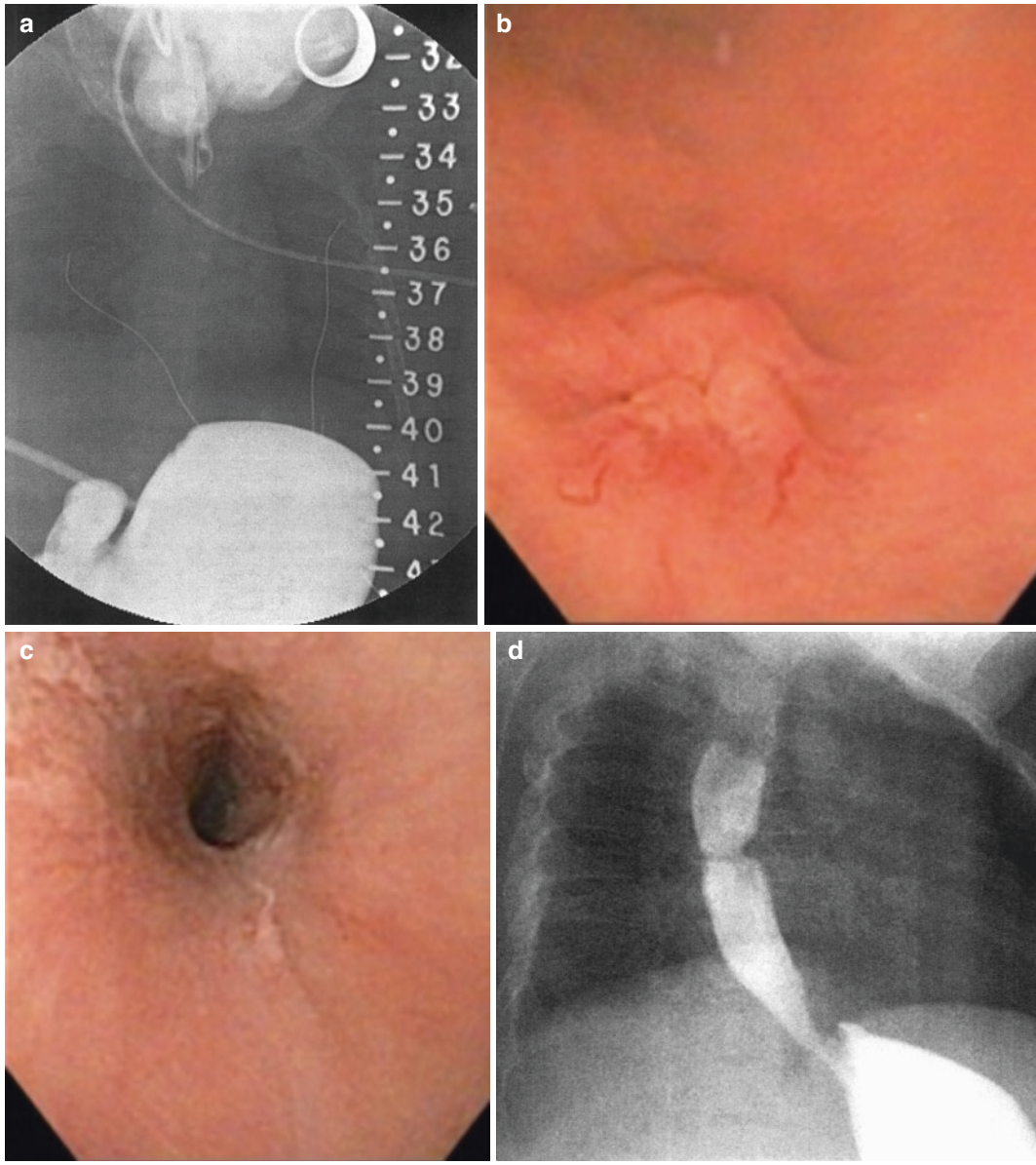


Fig. 24.13 (**a**) In another patient, a preoperative contrast study through the G-tube failed to provide any evidence for a lower esophagus. (**b**) Endoscopy provided more information on the possible lower esophageal segment. No lumen was seen and only a small amount of heaped up tissue, perhaps 4 mm in diameter, was found where the lumen should be. Through a transverse laparotomy incision, a nubbin of tissue, 3 mm long, was seen arising from the stomach high on the lesser curvature. A 7-0 horizontal mattress traction suture was placed in the nubbin and the suture tagged. By gently pulling up and down on the suture, the area of heaped up tissue was seen to move in an upward direction indicating it was part of the esophageal primordium. A second traction suture was placed and both were anchored in the diaphragmatic fascia to provide upward tension and initiate growth of the primordium. (**c**) After 2 weeks of internal traction, a short esophageal lumen could be seen endoscopically through the G-tube site. (**d**) After a little over 5 weeks, there was sufficient growth for a true primary repair. This contrast study was done after a subsequent fundoplication

nubbin (primordium) 3–4 mm in length or less and with little tissue strength or be relatively thick walled and reach nearly to the upper pouch. The structural variation of the segments will mean that the amount of tension applied will fall to the judgment of the surgeon.

The traction sutures must strike a balance between speeding growth and not exceeding tissue strength. The sutures occasionally pull out, which reinforces the need to avoid the lumen (Table 24.3). A traction suture(s) which pulls out with no leak from the lumen has minimal consequences. If more pull out, they will either have to be replaced or the esophageal anastomosis carried out. If growth is too slow, however, the esophageal segments can become encased in adhesions and progress stopped. The tension, therefore, should be increased at least daily to insure that growth will continue.

The optimal timing of the increases in tension also has not been worked out. At present we increase it daily or, even, twice daily by adding short pieces of silastic tubing under the traction sutures as described. This brings the stimulus to a maximum daily, but the response will largely dissipate the tension by the next day. Basic studies have indicated the biomechanical growth stimuli are most effective when intermittent rather than continuous [24, 29]. This principle may also apply to induced catch-up esophageal growth and an intermittent increase in tension may provide the best overall stimulus.

The current method has in its favor simplicity and practicality. Nevertheless, devices designed to increase tension at intervals may be beneficial and supplant this method. Improvements in the technique of growth induction will likely be made but the biological principles will remain the same.

Growth Induction: After Failed (Colon) Interposition Graft

Interposition grafts may fail or be unsatisfactory for one of three general reasons: inadequate blood supply, poor graft function, or developing an intrinsic disease. We have had two patients with colon interpositions which failed. One had a poor blood supply which quickly progressed to graft necrosis and was removed. The aperistaltic graft in the other patient progressively dilated causing significant dysphagia and aspiration. In both patients, a short lower esophageal segment was found on contrast study and judged to be satisfactory by endoscopy. Because the patients were 2 and 4 years old, respectively, the cervical esophagus was not closed but grown using the Kimura advancement technique [23]. In both, the lower segment was grown using external traction until a primary anastomosis was carried out. Both are now eating normally by mouth and the first patient is over 10 years old and 13 years old [30].

These two patients and along with an 8-year-old boy with a long congenital stricture treated by growth induction and resection indicate that the esophagus will respond to axial tension at least into childhood. This was predictable because even the smallest primordium has been programmed to develop into a normal esophagus and to shut this response down would likely require an elaborate and unnecessary genetic mechanism. Of interest of course is whether or not the growth response remains in adulthood?

Problems with Growth Induction

The techniques described used a flexible surgical approach to stimulate growth by axial tension and solve the long-gap problem. Importantly, the application of this biological principle has been effective across the full range of segment sizes encountered and well into childhood. Axial tension now has begun to be used worldwide, and a recent survey of attendees at a meeting of the British Association of Pediatric Surgeons revealed that growth induction was used by about 40 % of the pediatric surgeons to close a long gap [31]. The same study, however, reported that about 24 % of this group "were not entirely satisfied with the procedure."

The main difficulty with this method of growth induction is in accurately placing the

traction sutures and incorporating sufficient tissue to hold under tension yet avoiding the lumen and a leak. Effective suture placement becomes increasingly more difficult the smaller the esophageal segment and the more delicate the tissues. In our Minnesota experience, several sutures pulled out and some had to be redone. As expected, some sutures were moved higher on the chest wall (reconfigured) after growth had occurred to maintain the growth stimulus (Table 24.3). Both placing traction sutures and having them pull out, however, are new experiences for pediatric surgeons and will temper enthusiasm for the procedure until more experience is gained.

To maximize tension and the growth response usually also requires ventilator support in an intensive care unit and may require 2 or more weeks for completion. Finally, once growth is adequate, a second operation will be required. These difficulties, however, in our opinion, do not justify returning to gastric or colon interpositions for solutions to the long-gap problem.

There is no doubt that the technique of placing traction sutures and producing tension will be improved. Certainly, minimally invasive thoracoscopic techniques and technology will improve, although, at present, they seems more suitable for larger esophageal segments. Eventually, the techniques for growth induction will advance and be used more frequently with good results.

Among the technical points, we believe it is important to stay out of the lumen while inducing growth in order to avoid esophageal leaks. Consequently, we avoid using intraluminal devices which may produce pressure necrosis of the esophageal wall. The once heralded use of intraluminal magnets violates this principle and could lead to perforation [32]. This criticism can also be applied to the use of intraluminal hydrostatic pressure to enlarge the lower segment [33]. This technique produced necrosis of the entire lower esophageal segment with its use in one patient after the publication appeared. Certainly, intraluminal devices would not be satisfactory and not possible for the very small lower segments where the lumen may be tiny or even absent.

In summary, axial tension has been effective in inducing growth throughout the entire EA spectrum supporting it as the basic biomechanical stimulus which triggers the esophageal growth response [29]. Furthermore, application of this principle has demonstrated than an adequate developmental potential exists no matter how small the primordium.

Growth Induction: The Anastomosis

A true primary repair done across the EA spectrum, even including the common type C lesions, will require some anastomoses to be done under tension. Consequently, the construction of a reliable anastomosis will be important to both the early- and longer-term success of the LG-EA repair and to esophageal repairs in general.

The operative details of the anastomosis are based on the methods used by the author for the repair of the various forms of EA, usually LG-EA. Varying anastomotic techniques, however, are used by other surgeons with good results. The reader can evaluate the technical details and the reasoning behind them for our method in this chapter and decide which components they wish to incorporate into their repairs. Others have also used myotomies, created flaps, or partially pulled up the stomach to allow the anastomosis to be made. These methods have drawbacks, however, as has been discussed. The anastomosis described here will only be an end-to-end true primary repair [4, 19, 34, 35].

An anastomosis becomes more difficult to accomplish under one of three general conditions. The first, and the subject of this chapter, is when, for whatever reason, there is a significant gap between the two ends. The other two general problems are a discrepancy between the size (diameter) of the segments and, second, poor alignment of the edges that are to be joined together. The size discrepancy problem will be addressed in this section and alignment difficulties in Chap. 40: Redo Operations.

When the anastomosis is under tension because of a gap between the ends, an anasto-

motic leak or even disruption, as well as the later problems of stricture formation, GER, or recurrent tracheoesophageal fistula (recTEF) become more likely [36, 37]. These problems, moreover, may have chronic consequences and produce an unsatisfactory long-term outcome. For these reasons, both the anastomosis and the follow-up issues are important to achieving a good and durable result.

A true primary esophageal repair requires the esophageal segments to be long enough to accomplish an anastomosis, and the decision should be made before the ends are opened. Otherwise, if it is necessary to reclose them or bring the upper pouch out as a spit fistula, length will be lost, and it will be much less likely that a primary anastomosis will eventually be achieved. As discussed, by making the final assessment in the operating room, the best approach can be made for a successful outcome (Table 24.2).

With the decision that a primary repair is possible, the ends can be opened. To open the upper pouch, a round-tipped catheter is placed down it and kept on gentle pressure, allowing an opening to be made by cutting down on it with a #15 blade. This technique will avoid tissue damage caused by grasping the pouch. Finding the lower lumen, however, which is often narrow after a period of tension-induced growth, may be difficult, and length may be lost by multiple incisions into the lower esophagus (Fig. 24.11a, b). Threading a tube, wire, or even a thin endoscope up through the G-tube site into the lower segment will make finding the lumen much easier and make the opening cleaner.

The lower segment often tapers at the upper end, and cutting vertically downward along the outer curvature will effectively enlarge the anastomosis (Fig. 24.14a). The extent of the incision is limited by the effective increase in gap length it produces. The depth of the incision becomes the new gap length and must be considered. If the circumference discrepancy still exists after the vertical incision, the sutures should be evenly spaced to make up the difference, wider on the larger segment and closer on the narrow end.

Once the opening has been made, a stay stitch placed at the opposite corners from within the lumen outward will help stabilize the segment and facilitate subsequent suture placement. Again, to avoid tissue damage, a tissue forceps (pickup) is placed within the lumen and gently spread open without grasping the tissues, revealing the mucosa which is considerably lighter in color and readily identified.

The anastomotic sutures are placed in a square, full-thickness fashion, taking generous tissue bites and then tagged (Fig. 24.14a). To create an effective single-layer anastomosis, we prefer simple sutures carefully tied. A variety of two-layer anastomoses have been used beginning with the first repair by Cameron Height [38]. In the early days, anastomotic leaks were common with serious consequence and the two-layer repair attempted to prevent them. As technique improved, the more difficult strictures which were frequent in two-layer repairs became less acceptable, and surgeons switched to a single-layer anastomosis. As noted, however, leaks and recTEFs are still a problem; consequently, surgeons have tried a variety of suturing techniques. We believe simple sutures carefully tied off tension will provide the best results. Such techniques as horizontal mattress sutures may produce necrosis of trapped esophageal wall and do not seem to be satisfactory [39].

For an anastomosis under tension, the back row of sutures is placed to be tied on the inside with the corner sutures configured for tying on the outside. The gap and the amount of tension necessary to bring the ends together will determine how the sutures are tied. If there is not much tension, the back row, except the end sutures, are tied and cut close to the knot. The end sutures are not tied to allow mobility for the placement of the anterior row of sutures (Fig. 24.14b). The anterior sutures are tied after a small caliber catheter (8–12 French) is passed down from above through the anastomosis. The tube is removed within 12–24 h so it does not produce pressure injury of the esophagus.

Closure is done after a chest tube is placed and loosely anchored to the parietal pleura to prevent

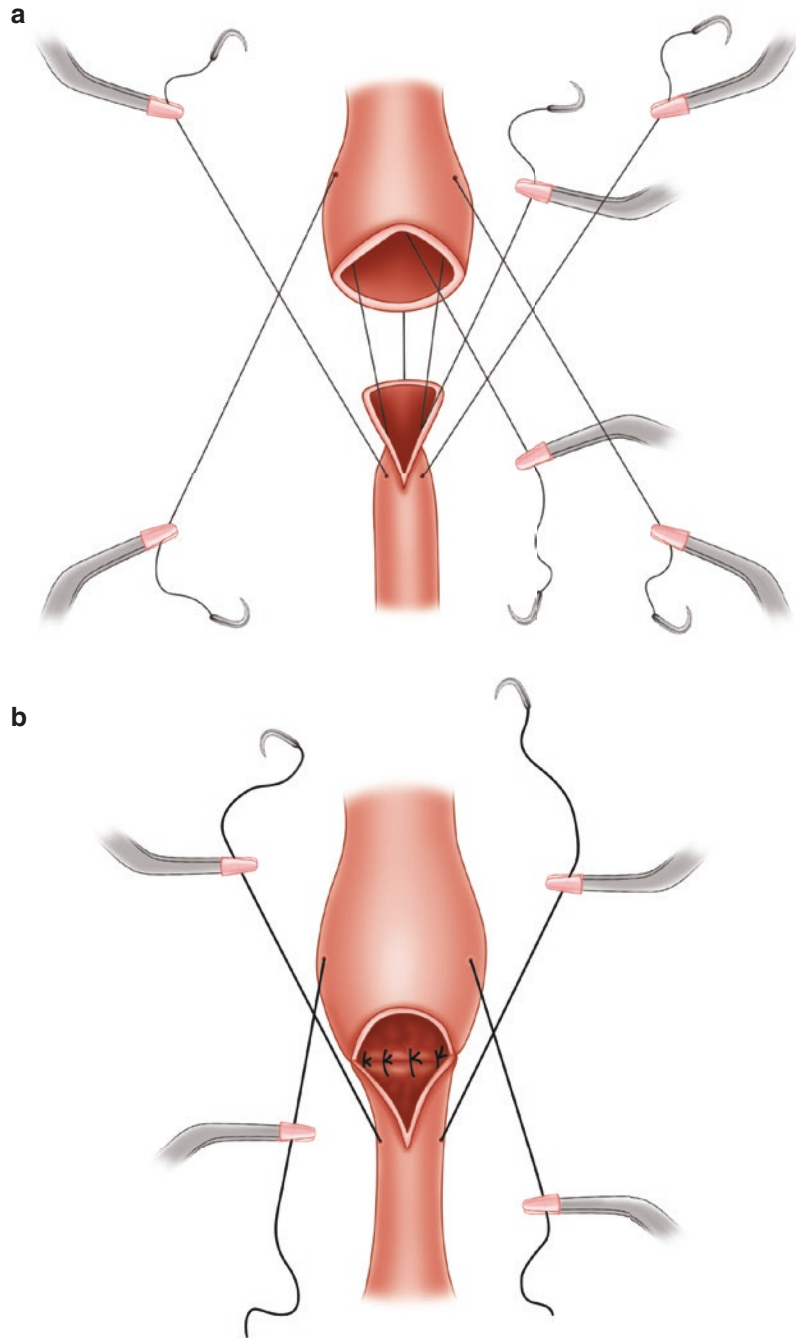


Fig. 24.14 (**a**) For an anastomosis when a gap remains between the opened upper and lower segments, the back row of sutures is placed and each end tagged with shod, small clamps and crossed. Typically, six to eight sutures are placed first. Notice that generous bites of esophagus are taken. Note the narrower lower segment has been cut back to effectively enlarge the anastomotic circumference. This incision, however, also effectively lengthens the gap and, therefore, must be limited in extent. The sutures should be evenly spaced according to circumference, wider on the larger and closer on the smaller opening. (**b**) The crossed sutures are used to gradually pull the ends together. When the ends are touching, one suture pair is freed up and carefully tied while tension remains on the crossed suture pairs. In this way, the individual sutures are tied off tension in an anastomosis that may end up under tension

direct contact with the esophageal anastomosis. The ribs are looped loosely by a pericostal suture and a normal space is left between the ribs which help prevent fusion. In addition, we often place sheets of very thin silastic sheeting between the ribs to hinder fusion.

For the more difficult anastomosis, when pulling the crossed dissecting sutures does not bring the ends together easily and/or the anastomotic sutures will be under tension, a period of traction in the operating room will be very helpful (Moderate Gap, Table 24.2). The back row of sutures are placed as before, tagged individually, and crossed. Slowly pulling on the tagged sutures will increase the tension and bring the edges together over a number of minutes. Once the edges are touching, tension is maintained on all sutures except for one pair at a time which is peeled off and tied without tension, and, therefore, the sutures are much less likely to tear through the esophageal tissues. As the tying proceeds, the tension holding the esophageal ends together is transferred from the untied to the tied sutures. This is an effective way to create a well-constructed and reliable anastomosis despite moderate tension, and in the overall Minnesota experience, no clinically evident leaks occurred [4, 6, 19, 34, 35].

When the tension required to complete the anastomosis is even greater, an additional advanced technique is to use small peanut sponges and even thumb sponges held by clamps to push the segments together while also pulling on the crossed sutures. Once together, the crossed sutures will be used to hold the ends together for several minutes, allowing the tension to somewhat dissipate. This period of traction and holding will also allow individual pairs to be tied off tension. An anastomosis in this setting will be under significant tension and both the generous tissue bites and the tying will have to be carefully done. It is emphasized that this maneuver is only for the most experienced surgeons and, again, argues for the very difficult cases being done at established centers.

We have used 5-0 or 6-0 nonabsorbable, monofilament (Prolene) sutures for the anastomosis, because they are essentially nonreactive. These sutures also help to maintain anastomotic integrity during the subsequent dilations which are done (gently) as soon as 2–3 weeks later. The sutures are only very slowly sloughed into the lumen, and for early endoscopic examinations, they will be quite visible even when using only 4–5 throws and cut close to the knot. After 6 weeks or more, the endoscopist can often pull some out or shorten the ends.

Making the Choice in Very Long-Gap EA: Growth Induction or Interposition Graft

As shown, growth can be reliably induced in the smallest esophageal segments and produce an outwardly normal esophagus. The function even with disordered contractions below the anastomotic site will be satisfactory and equivalent to the common EA-TEF repair. The time required for adequate growth will be roughly in inverse proportion to the starting gap length, and, at a minimum, a period of 6–7 days and two operations will be required. When starting with a primordium, growth may require 4 or more weeks and additional procedures may be necessary to reconfigure the traction sutures. Consequently, the question will be whether or not this approach is worth it in the long run. In our opinion, it clearly is, with the important realization that GER and post anastomotic strictures must be addressed. It must also be recognized that recent national studies have shown that even adults with short gap EA (type C) repaired in infancy frequently have problems with dysphagia and reflux, indicating that these are issues that often must be followed and treated for the long term across the entire EA spectrum (Entire section on: The Active Pursuit of Normalcy; Chaps. 43: Aronson; 44: Rintala).

If these issues are effectively treated, the children will do very well indeed and essentially all will eat normally and as well as their siblings. Most importantly for the LG-EA children, there is no reason to suspect late deterioration and failure of the esophagus grown by tension.

This predicted long-term outcome is in sharp contrast to either a colon interposition or a gastric pull-up, both of which fall heir to a variety of problems, increasingly difficult to solve with time. The gastric interposition is an alternative which is instructive because the surgical techniques have been well worked out [40]. Initially, a cervical, "spit" fistula and a G-tube are placed, and when the child reaches suitable size, it is usually a one-stage reconstruction. A comparison with the Foker procedure might seem favorable early with usually these two operations completed typically by 1–2 years of age for the gastric pull-up.

What it also brings, however, are severe consequences for the short and, especially, the long term. Initially, there will be feeding difficulties as dumping problems will exist to some degree. Many small meals, low weight gain, and, apparently, universal anemia become part of the new chronic disease constellation [40]. Frequent aspiration may be common and lung disease becomes a significant possibility. For the longer term, the obligatory reflux of a high gastroesophageal anastomosis will produce cervical esophagitis and eventually Barrett's esophagus and beyond [41]. The gastric tissue can be wrapped to hinder reflux, but the wrap will be at the thoracic inlet and difficult to fashion adequately. In addition, gastric atrophy and atrophic gastritis may also develop and these changes too are a precancerous condition. The short term is predictable and can be acceptable but difficulties will increase with time.

Colon interpositions are also beset with chronic problems and because this interposition will lack peristalsis, it frequently dilates and chronic aspiration becomes common. Although about half of these patients are satisfactory after 20 years, the rest are not and with the colon being heir to a variety of diseases, additional problems should be expected later [42].

Seventy good years appears very unlikely for either of these interpositions. This goal, however, is only beginning to weigh on the surgeon and the pediatric world in general. For the surgeon, peace of mind as well as reputation depends on fewer early complications and shorter lengths of stay (LOS) rather than events which may occur 10 or even 30 years later. A somewhat cynical but often accurate statement would be that for many pediatric caregivers, their patient's life ends at 16 years of age. Despite the fact that there is significant evidence that this is not true, one goal seems to be to hand off the teenage patients with them apparently "doing well."

Esophageal growth induction, however, can be reliably done at 3.5 kg, and if the lower segment is 2 cm or more long, then the growth time will vary from 1 to 3 weeks and is typically well tolerated. The anastomosis is frequently followed, however, by a fundoplication and a series of dilations. Nevertheless, once completed, these patients typically eat normally and progress well and fulfill the adage that "one's own esophagus is best" [43]. Currently, growth induction has been successfully used worldwide in small numbers of cases, and it seems likely that larger series of cases will appear [25, 26, 44–48]. For the longer term, moreover, the advantage seems to clearly be with growth induction. Long-term results are certainly needed, but the growth-induced esophagus should not deteriorate although it will need to be followed for later reflux and dysphagia. Among the interpositions only a jejunal graft seems to have satisfactory stability and, if necessary, would be the best interposition choice [49].

The decision between growth induction and an interposition graft for LG-EA will depend on a number of important considerations and eventually will depend on the longer-term results. Clinical comparisons are better made when there is one variable or at most, a few which can be adequately controlled in the study. The comparison under discussion, however, involves an uncountable number of variables, and, therefore, the answer will need to be based on at least a 10- or 20-year follow-up as an adequate approximation to the long-term goal of 70 good years.

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Thoracoscopic Elongation of the Esophagus in Long-Gap Esophageal Atresia

25

David C. van der Zee

Introduction

Esophageal atresia has always been the hallmark of pediatric surgery. Long-gap esophageal atresia (LGEA) has been a challenge for many pediatric surgeons for many decades. Several alternative techniques have past the revenue, some to stay, and some to go. As early as in the late 1950s of the past century, Rehbein [1] already described the approximation of both ends with two metal balls in the esophagus attached to a thread in between the two ends that were slowly pushed to one another.

The fact that many different procedures have been developed over the years since indicates that the procedures do not have a guaranteed adequate success rates, and in many instances, it was wise to postpone treatment until the child was somewhat older. Meanwhile the child was either given a spit fistula or there should be continuous suction from the proximal esophagus to prevent aspiration, requiring intensive nursing care.

Two main principles are at hand when to decide which technique will be used. A popular technique that has been used over the years is the replacement of the esophagus with either the stomach, jejunum, or colon [2–4]. Others advocate that the original esophagus is always the best and pursue techniques that will result in elongation of the esophagus [5]. Whatever technique is used, there will always be two ends put together that were not tuned to each other, and motility disorders will occur in either technique.

In 1997, John Foker et al. [5] published an article in which they described a technique in which they approximated the two ends of the esophagus with traction sutures that were brought outside, and with traction, the two ends could be approximated and a delayed primary anastomosis could be made. They hypothesized that traction and growth were responsible for the elongation. Some other publications followed with similar good results.

With the advent of minimal invasive surgery, it was just a matter of time before the first publications came with results from thoracoscopic repair of esophageal atresia. In 2005 Holcomb et al. [6] published the results from a multicenter study where 103 children had undergone thoracoscopic repair of their esophageal atresia. In 2007, van der Zee and Bax [7] published a single center study on 51 neonates with thoracoscopic repair of type C esophageal atresia.

With increasing experience in the thoracoscopic repair of esophageal atresia, it was a logical step to attempt a thoracoscopic approach to the repair of LGEA.

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In 2007, van der Zee et al. [8] published the technique of thoracoscopic elongation of the esophagus in LGEA.

In this chapter, the technique will be described and the results will be discussed of thoracoscopic repair of LGEA.

Technique

After the general work-up for VACTERL association, the principal first step in LGEA is to make a (laparoscopic) gastrostomy for feeding and to perform a contrast study to determine the length of the distal esophagus. Principally one could keep the child on parenteral nutrition during the process of the elongation procedure, but enteral feeding is preferred and has the benefit of gastroenteral stimulation.

With the aid of the Replogle tube in the proximal esophagus, the length of the proximal esophagus can be determined.

There is no strict age or weight limit.

For the procedure, the child is put in left semiprone position, with a support under the left arm pit to avoid compression of the vasculature. The right arm is extended over the head.

In some centers, the procedure is preceded by a bronchoscopy to determine or exclude a proximal fistula.

A 5 mm trocar is placed approximately 1 cm. below and anterior of the scapula point for the optic device. Two 3 mm trocars are placed in a triangle around the first trocar, as far apart as possible to avoid entangling.

CO2 insufflation is started with 5 mmHg pressure and a flow of 2 lt/m. It is waited for the anesthesiologist to settle the ventilation satisfactory. Usually this means that the frequency needs to be turned up.

By pushing gently with two 3 mm. graspers on the lung desufflation of the lung is accomplished. When and only when adequate view is obtained, the proximal and distal esophagus can be identified. When insufficient desufflation is obtained, a fourth 3 mm. trocar can be introduced with a flexible retractor to carefully press down the lung as far is necessary for adequate view.

It is started with the mobilization of the proximal esophagus up to the thoracic aperture (Fig. 25.1). It is important to determine that there is no proximal fistula; otherwise, this should be dealt with. In general, it is possible to close the proximal fistula thoracoscopically, but when the fistula is too high up in the neck, this should be done from the neck.

Then the distal esophagus can be mobilized under control of the vagal nerve, if necessary down into the hiatus (Fig. 25.2).

As the esophagus naturally lies in the posterior mediastinum, the traction sutures should be brought out as much posteriorly as possible to maintain its course, as well as the sutures not interfering too much with the lung after insufflations of the lung at the end of the procedure.

An Endoclose® device is used to introduce Vicryl® 4×0 sutures together with the needle (Fig. 25.3). For this purpose, a tiny skin incision is made at a level, either maximal cranial next to the scapula or caudal next to the spine. In total four sutures are laid at four corners of both the proximal and distal esophagus and pulled out again with the same Endoclose® (Figs. 25.4 and 25.5). A small silicone tube is used to bring the four sutures together and above this tubing traction is carried out with a mini-mosquito clamp. At the top of both the proximal and distal esophagus, a metal clip is attached to the sutures to allow for radiological determination of the progress of the elongation over the coming days.

After finishing the first procedure, the trocars are removed and the defects are closed with Vicryl® 5×0 sutures and Steri-strips® (Fig. 25.6).

Postoperatively, the child is extubated and only remained on light sedatives. Feeding is started the next day via the gastrostomy. Twice daily the sutures are checked for patency and traction is reinstalled on the sutures. Once daily a plain X-ray of the thorax is performed to determine the position of the clips.

When the clips have approximated sufficiently, a second procedure is executed. The patient is put in a similar position and the trocars are reinstalled. The amount of adhesions usually is limited and can be released without great difficulty. By releasing the tension from

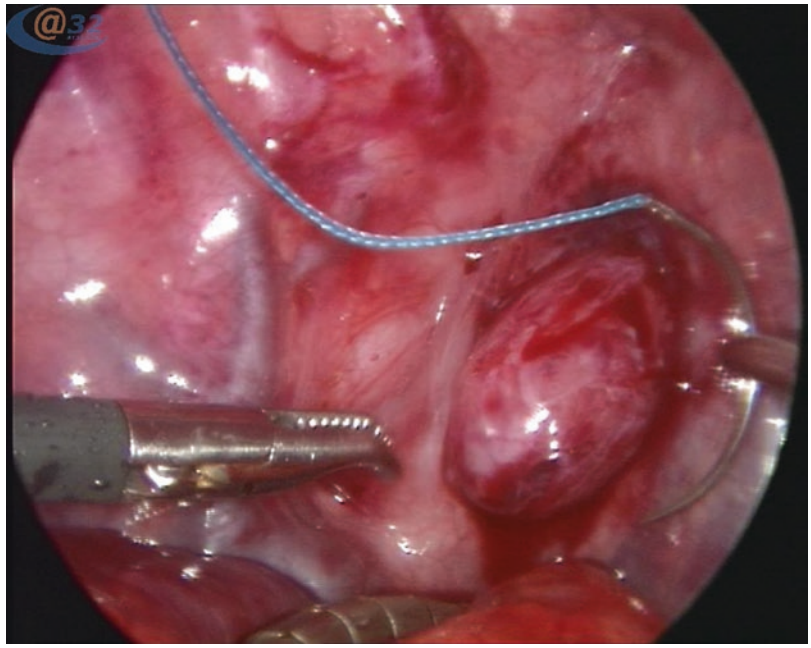

Fig. 25.1 Mobilization of proximal esophagus

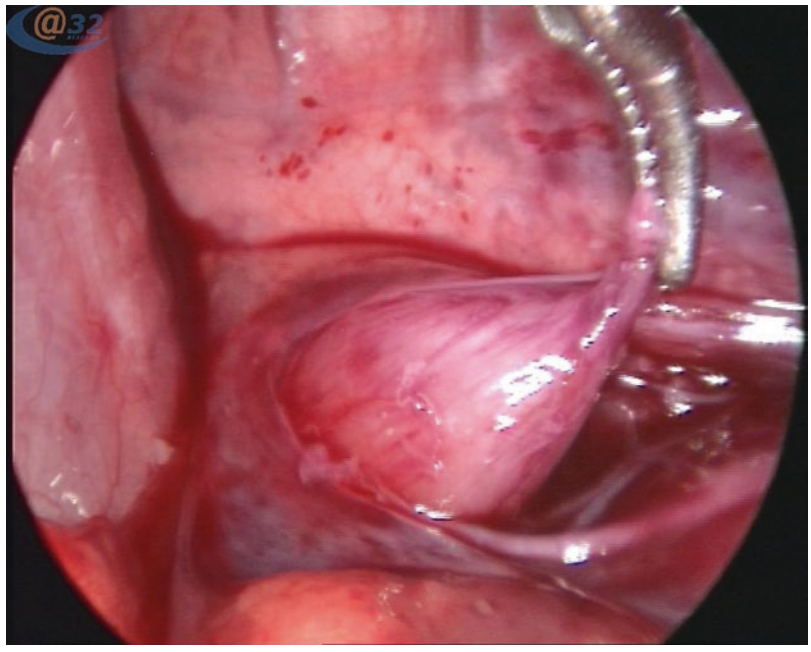

Fig. 25.2 Mobilization of distal esophagus

the outside sutures, it can be determined whether the esophageal ends can be approximated sufficiently at the level of the posterior mediastinum (Fig. 25.7).

The traction sutures are cut and taken down. Vicryl®5×0 sutures are used for the anastomosis. The esophageal ends are cut open with scissors, and the first one, two, or even three sutures are

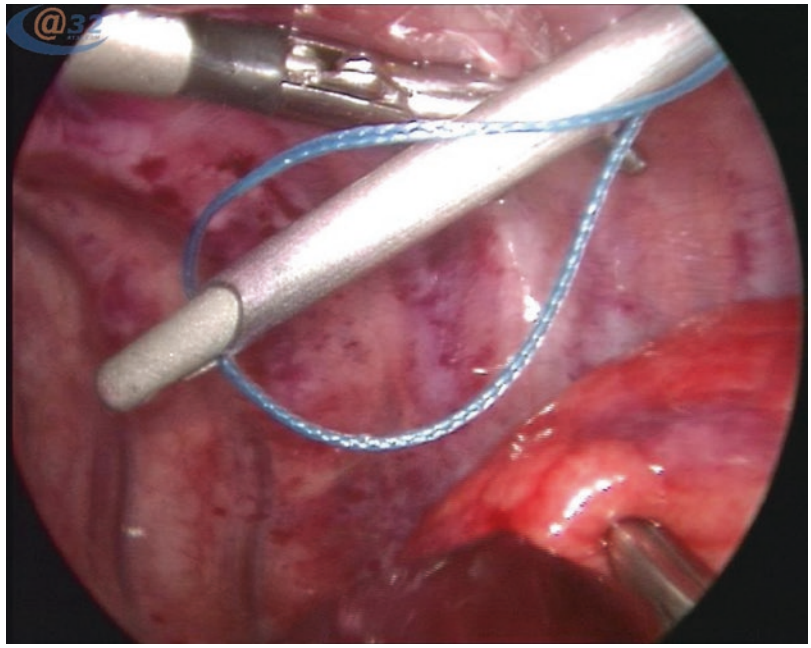

Fig. 25.3 The use of an Endoclose® to introduce a Vicryl® 4×0 suture and needle

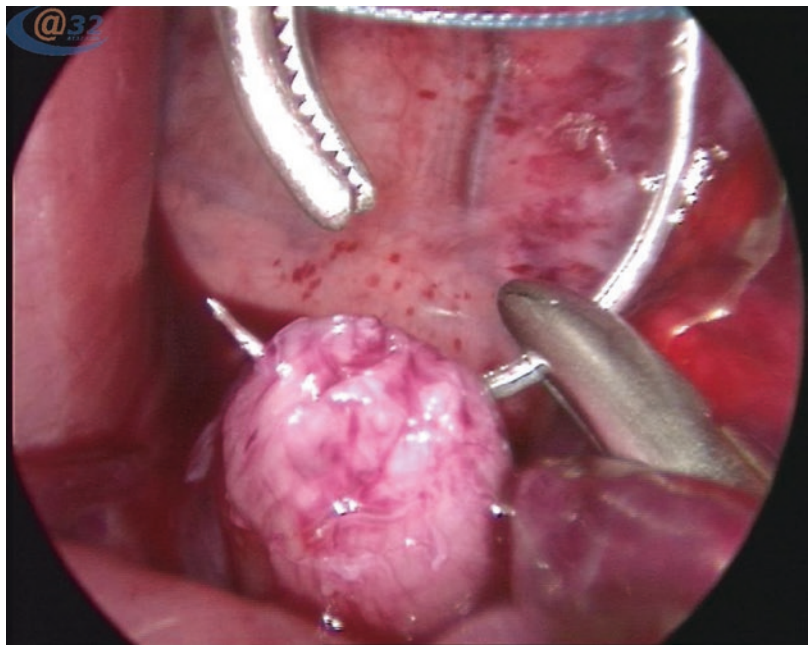

Fig. 25.4 Placing of first suture in distal esophagus

laid with a sliding knot to slowly approximate the proximal and distal esophagus. Thereafter, additional sutures are laid to complete first the posterior wall and introduce a 6F silicone nasogastric tube and then finish the anterior anastomosis (Fig. 25.8).

The trocars are removed and the defects are closed using Vicryl®4×0.

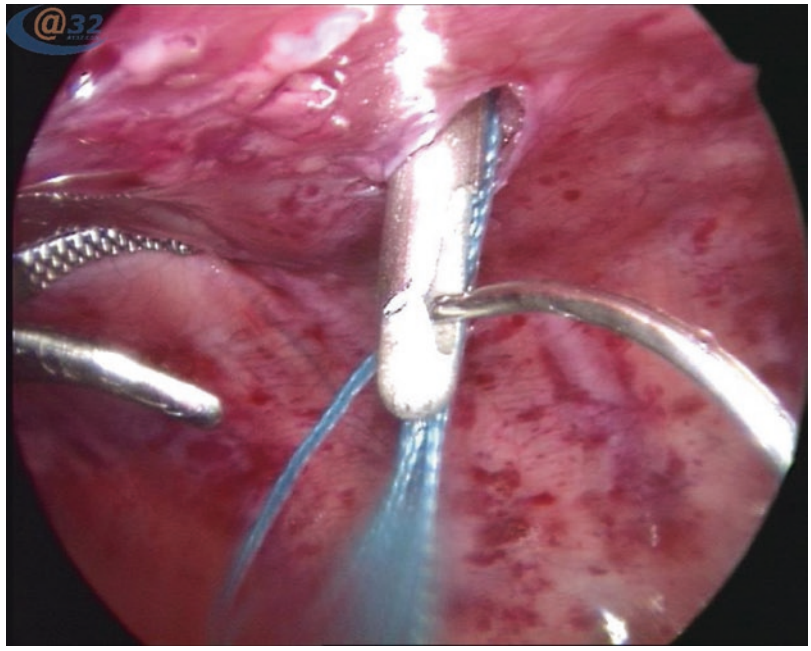

Fig. 25.5 Retrieval of suture and needle with the use of an Endoclose®

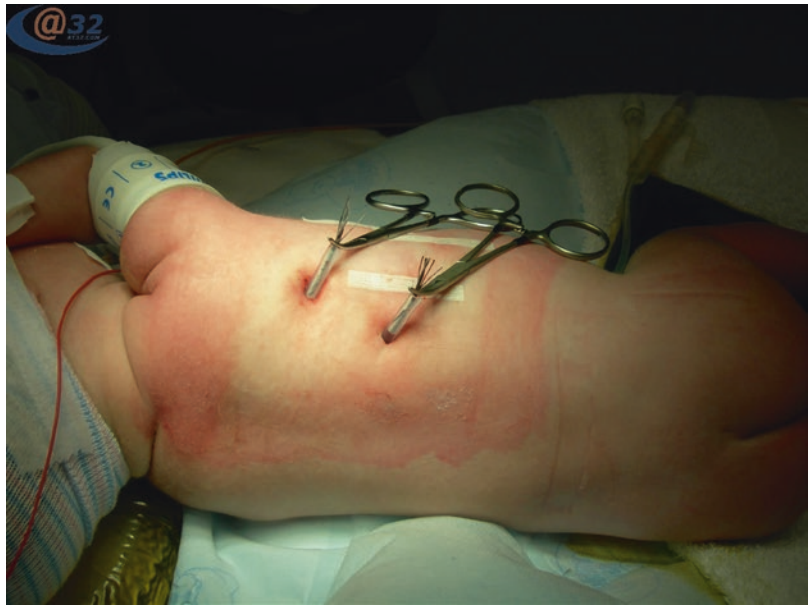

Fig. 25.6 Sutures are placed under traction over a Silicone tube

The child is extubated and kept on mild sedatives for the first 2–3 days. Antacids and prokinetics are started.

Gastric tube feeding is usually started after 2 days, although gastroesophageal reflux is frequently occurring, necessitating the gastrostomy feeding tube to be advanced into the duodenum.

After 5 days, an esophageal contrast study is performed to determine the patency of the esoph-

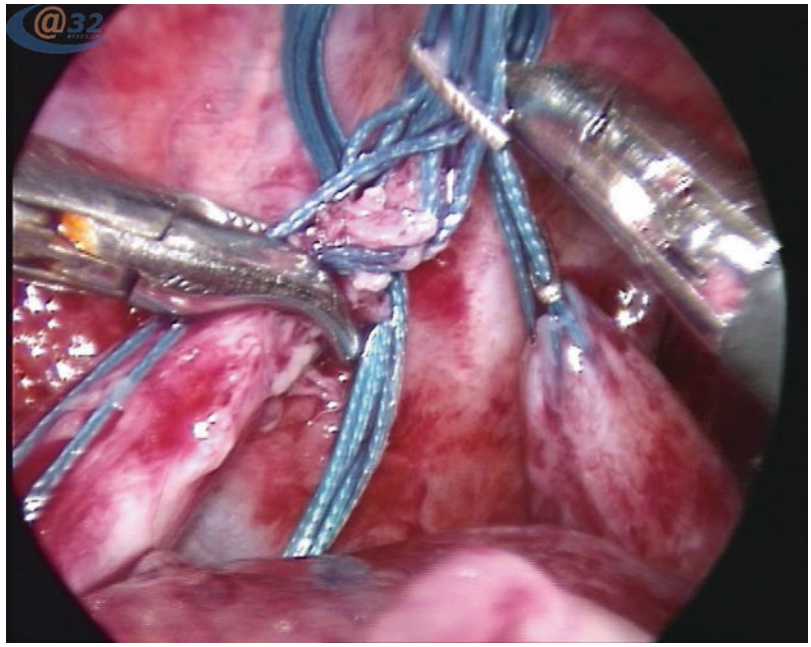

Fig. 25.7 Both ends of the esophagus have approached each other sufficiently to perform a delayed primary anastomosis

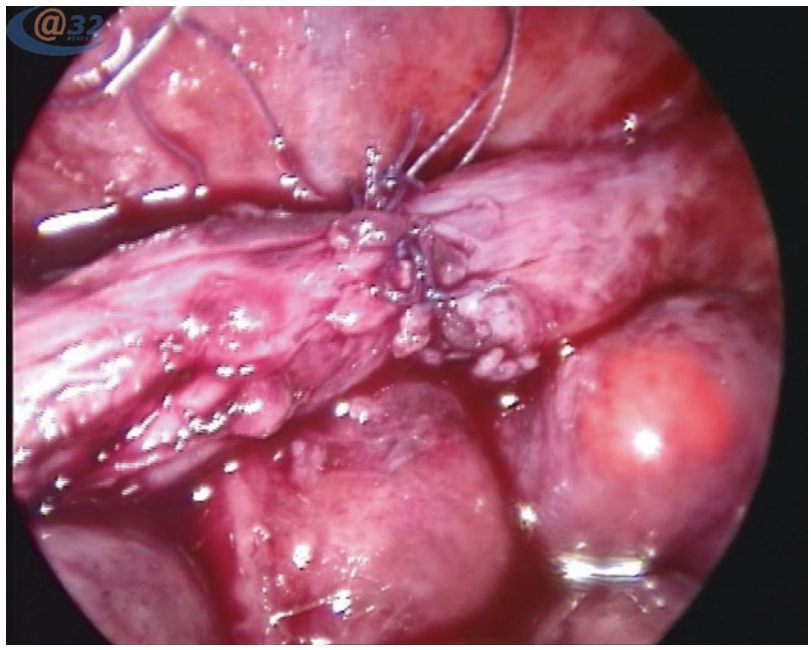

Fig. 25.8 Result after delayed primary anastomosis of proximal and distal esophagus

agus. When there is no leakage, oral feeding can be progressively started.

When the child is on full oral feeding, it can be discharged from the hospital.

The child is seen at the outpatient department every second week for the first 6 weeks. Thereafter, the follow-up is extended up to 1, 3, 6, and 12 months.

Complications

Preoperative

When a proximal fistula is present, the child can suffer from pulmonary complications. Many institutions advocate early trachea-bronchoscopy to exclude a proximal fistula.

The child can also present with complications from comorbidity, such as cardiovascular disease.

Intraoperative

Rupture of the traction sutures may occur. If this happens, the child needs to be taken back to the operating room to replace the traction sutures. However, when due to this complication one of the esophageal ends has ruptured, it is advised to abandon this technique and go back to one of the other alternative techniques, like gastric pull-up or jejunal interposition.

Postoperative

When an anastomosis is made under tension, the risk for anastomotic leakage is present. When leakage occurs, it usually suffices to place an intrathoracic drain, preferably through one of the trocar holes. Over a few days, the leakage stops spontaneously, and the drain can be withdrawn afterward.

In case a small residual diverticulum persists, this can usually be treated conservatively, as long as there are no sequelae from the diverticulum. Otherwise the diverticulum can be resected thoracoscopically at a later stage.

Usually esophageal stenosis occurs, in spite of the antireflux medication, necessitating esophageal dilatation, the first 2–3 weeks postoperatively. When recurrence of esophageal stenosis persists, a laparoscopic antireflux procedure can be planned between 4 and 6 weeks postoperatively.

Own Results

Between 2007 and 2009, there were four children with a long-gap esophageal atresia that were presented to our department.

The first child was born prematurely at 32 weeks of gestation with a birth weight of 1,500 g. She soon after birth showed signs of aspiration, due to a proximal fistula.

We initially deemed the child too small for a first case of thoracoscopic elongation; thus, we performed a thoracoscopic closure of the proximal fistula as a first step.

Four weeks later at 36 weeks of gestation and 2,000 g, she underwent the thoracoscopic elongation. She endured the procedure without any problem.

During postoperative follow-up over the next days, the clips approached each other progressively; until on the fourth day, the distal traction sutures came out, after a change of position in the crib. She was taken into theater and new traction sutures were placed.

After another 2 days, the esophageal ends had approximated sufficiently to perform a delayed primary anastomosis without complications.

At the contrast study on day 5, there was some minor extravasation of contrast at the site of the anastomosis. The feeding over the gastrostomy was continued for another 3 days after which oral feeding was started without complications.

Ten days after surgery, she was discharged from the hospital.

At follow-up after 2 weeks, she had developed an esophageal stenosis, which was dilated up to

F8. After 2 weeks at planned endoscopy, she showed a renewed stenosis that was dilated up to F10. After dilatation, the stenosis could be passed with the endoscope and a large hiatal hernia was seen.

She was therefore planned for a laparoscopic antireflux procedure 1 week later, at which occasion the esophagus was dilated again up to F10.

Thereafter, she required no more dilations and now is 3 years old and eating all that is offered without any restrictions. She has a normal development and length and weight are according to her age.

The second child was a term born boy with a weight of 3,500 g. There were no other anomalies. He underwent the first step of the procedure at the age of 3 days without any complication. After 3 days, the sutures form the distal esophagus came out and he was taken back into surgery. At renewed thoracoscopy, there were few adhesions, but the distal esophagus had been torn open. Closure of the rupture would increase the distance again and new sutures would have to be placed at the site of the rupture. Also because it was the distal esophagus, there was an increased risk of infection. It was therefore decided to close the rupture in the distal esophagus and abandon the thoracoscopic elongation procedure.

He was put on antibiotics for 5 days and underwent a jejunal interposition 2 weeks later.

The boy is now 2½ years old, has a normal development, and is eating everything with the family without restriction.

A third child came to us from abroad at the age of 5 months with a weight of only 3,800 g. She had a gastrostomy for feeding and a suction tube in the proximal esophagus.

After inventarization, she underwent the first step thoracoscopy without any complication. Because of her malnutrition, she was fed intravenously and kept on the ventilator postoperatively while mildly sedated.

After 5 days, the esophageal ends had approximated sufficiently for thoracoscopic delayed primary anastomosis. She underwent the procedure without complications, although the anastomosis had been made under considerable tension.

On the fifth postoperative day, she developed leakage with pleural effusion for which a thoracic tube was placed. On starting gastrostomy feeding, the milk came out of the drain. The feeding tube was therefore advanced into the duodenum and feeding was accepted.

The drain was productive for 5 days after which it could slowly be withdrawn and removed after 10 days. On contrast study, there remained a small sinus at the site of the anastomosis, which gave no clinical symptoms. After 15 days, the mother could give her daughter the first bottle feeding in 6 months (Fig. 25.9).

After 4 weeks, she underwent a laparoscopic antireflux procedure for recurrent stenosis. The small sinus remained unchanged.

After they returned to their home country, she has had some more dilations to maximize the diameter, in order not to increase the pressure on the diverticulum and with that have the risk of increasing the size.

She is now 1½ years after the procedure and eating well. Her length and weight have improved considerably after the operation.

The fourth child also came from abroad and had undergone multiple prior attempts on open Foker procedure elsewhere without success. As he came to us, he was 2 years old, weighing 12 kg.

He had a spit fistula after several attempts of Kimura elongation of the proximal esophagus.

After mobilizing the proximal end, the esophagus merely just reached up to the thoracic aperture.

When opening up the thorax, it became apparent that the whole esophagus had changed into solid scar tissue without any patency. It was decided to make a jejunal interposition, of which the proximal anastomosis could just be made inside the thoracic aperture.

The postoperative course was without complications and he could be discharged after 2×s. He is now over 1 year after the jejunal interposition and eating a normal diet with the rest of the family (Fig. 25.10).

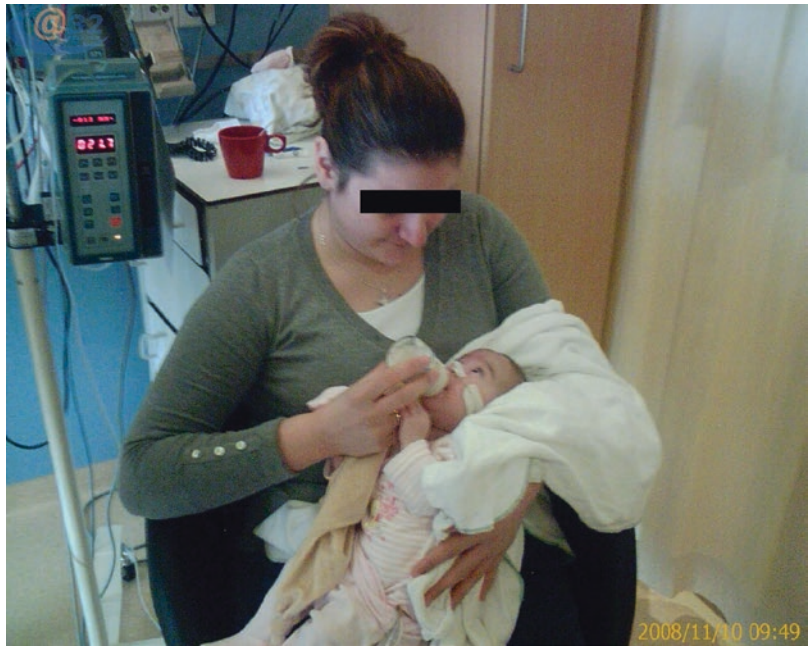

Fig. 25.9 Third patient receiving first bottle feeding after delayed primary anastomosis at the age of 5 months

Fig. 25.10 Patients three and four 2 and 1½ years after operation, respectively, during encounter at airport abroad

Discussion

Long-gap esophageal atresia, i.e., without a distal fistula, has always been a challenge for pediatric surgeons. In a recent survey by Ron et al. [9] in the UK, the majority of pediatric surgeons would either choose for a gastric pull-up or perform the Foker technique for long-gap esophageal atresia.

With regard to the thoracoscopic approach of esophageal atresia with trachea-esophageal fistula, about half of the pediatric surgeon had experience in endoscopic surgery, but only a small percentage

had experience with thoracoscopic repair of esophageal atresia. On the other hand, about three-quarters of them is considering on starting on thoracoscopic repair of esophageal atresia.

The thoracoscopic repair of long-gap esophageal atresia, however, is of another dimension.

It requires expert skills in endoscopic dissection and suturing, often under considerable tension. In case complications occur, a broad armamentarium of alternative techniques should be available to deal with the problems and bring the procedure to a good end.

It is known from aviation that airplane crashed always are a resultant of multiple mistakes and/or misjudgments. The (thoracoscopic) Foker technique can give excellent results, if all goes well. However, if complications do occur, there should be a low threshold to change to alternative techniques. Therefore, the thoracoscopic Foker technique should be foreclosed to a limited number of centers of expertise.

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26 Perioperative Management of the Esophageal Growth Procedure

Michael Sweeney

Introduction

Pediatric patients with long-gap esophageal atresia (LGEA) pose a series of problems from the perioperative management of the growth procedure through the surgical repair and later in learning to eat. What constitutes LGEA is not precisely defined but is at least a gap of 2–3 cm or greater. Ultimately, of course, it is in the eye of the beholder who must accomplish the anastomosis initially or first grow the esophageal ends. The growth approach to long-gap esophageal atresia has the goal of a primary esophageal repair and to ultimately achieve normal esophageal eating and drinking, avoiding a "chronic illness" syndrome [1, 2]. This process, however, can be long and sometimes difficult and is best achieved through a collaborative approach among dedicated surgeons, anesthesiologists, gastroenterologists, otolaryngologists, anesthesiologists, intensivists, nurses, respiratory therapists, radiologists, rehabilitation specialists, social services, and the family.

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The incidence of esophageal atresia with/without tracheoesophageal fistula (TEF) has remained fairly constant since 1948 [3] at around 1:3,500 live births with type A accounting for 4.87–7.7 % and type B between 0.5 % and 2 % (although Klaas et al. recently published the incidence of type B as high as 5.69 %) [3]. Between 10 % and 40 % of these infants will be diagnosed prenatally with the remainder diagnosed shortly after birth [4–6]. Initial stabilization is aimed at decreasing the risk of aspiration and preventing gastric distension/perforation. Positioning prone or with the head of the bed (HOB) elevated 30° and keeping the upper pouch free of secretions is necessary to preventing aspiration and pulmonary injury that can occur in the face of chronic aspiration [7]. To avoid gastric distension in the face of a TEF, positive pressure ventilation should be controlled and ventilation by bagging should be avoided [8]. The serious nature of the other defects that may be associated with EA means that surgical palliation including TEF ligation, gastrostomy, pharyngocutaneous fistula creation, cardiovascular (CV) surgery, and occasionally tracheostomy may be necessary before more extensive work-ups are completed. Ideally enteral nutrition should be provided via a gastrostomy tube (G-tube) prior to staged long-gap repair; however, if that is not an option, parental nutrition should be given [9, 10].

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Preoperative Preparation

The initial evaluation of infants presenting with EA must be thorough, as 50–70 % have associated anomalies [11–13]. In addition to detailed esophagrams to delineate the esophageal gap length and the presence or absence of a TEF, radiological studies must look at associated limb, rib, and/or vertebral anomalies. Gastroenterology studies should be performed or reviewed to identify associated anal defects, duodenal atresia, and malrotation or pancreatic anomalies. A renal work-up to detect kidney abnormalities and/or urethral/uretal anomalies should be completed. Detailed cardiac echo must be undertaken to evaluate for the presence of congenital heart defects and reveal the side of the aortic arch [13]. Approximately 10 % of these children will meet diagnostic criteria as either VATER, VACTERL, or CHARGE association and warrant a genetic consult [14].

If the child is referred in from another facility, records of all prior surgical procedures, anesthesia records, and inpatient experiences should be available for review for a meticulous preoperative evaluation. This should help avoid undesirable surprises and unnecessary problems in the areas of airway management, mechanical ventilation, hemodynamic stability, genitourinary anatomy, and pharmacological dosing. These data should then be reviewed with the team as well as the parents and a treatment plan developed tailored to the individual child. The patients should be screened for any acute or chronic condition or infection that is not optimally managed. Steps are then taken to correct identified problems and optimize the overall patient condition prior to the operating room.

Studies should include at a minimum, a baseline hemoglobin level should and packed red blood cells made available for transfusion because there is a small but definite chance for rapid intraoperative blood loss. If the child has been on total parental nutrition (TPN), a complete chemistry panel should be reviewed and the liver function determined. In the event of any bleeding concerns, a coagulation panel should be completed and any abnormalities corrected prior to surgery. Prior to anesthesia, a baseline 12-lead EKG can be helpful especially in children with congenital heart disease (CHD), and a recent chest radiograph (CXR) is desirable as well as an airway evaluation if there is concern for underlying tracheomalacia which is common in EA patients [2, 3, 15–17].

The Esophageal Growth Operation: Anesthesia Considerations

The first stage growth procedure is typically done around 2–3 months of age at a minimum of 3.5 kg, although can be undertaken at any age [2]. If the child has had prior medical or surgical procedures, the operative notes should be reviewed just prior to the first stage so unexpected findings are avoided. The first stage of the growth procedure is typically done through a right lateral thoracotomy with the patient in the left lateral decubitus position. If a cervical esophagostomy is present and will be relocated or oversewn and internalized, the neck and right arm should also be prepped in to allow manipulation of the esophagus at the neck and through the thoracotomy opening simultaneously. The G-tube should be removed prior to prepping to allow lower pouch esophagoscopy during the procedure if desired or to allow placement of a Red Robinson catheter up the lower pouch to facilitate repair.

All routine general anesthetic (GA) monitoring can usually be established prior to GA. The upper airway is frequently laden with saliva of varying amounts and viscosity and should be thoroughly cleansed and evacuated with suction prior to induction of GA. This suctioning will prevent excessive tracheobronchial aspiration prior to endotracheal (ET) intubation.

Induction may be inhaled sevoflurane or intravenous (IV) agent if reliable IV access is available, at the discretion of the anesthesiologist. Neuromuscular (NM) blockade is generally used to facilitate tube placement, with IV atropine and lidocaine to blunt unwanted autonomic and reflex reactions to ET intubation such as bradycardia and bronchospasm. Additional suctioning is usually needed during direct laryngoscopy. A cuffed ET tube is useful because of the reduced total respiratory dynamic compliance during the intra-

and postoperative periods. Because of the need for future prolonged positive pressure ventilation on the pediatric intensive care unit (PICU), the recently developed Microcuff® ET tube is preferred at our institution, for prevention of chronic subglottic complications as well as nosocomial pneumonia. The tip of the ET tube is positioned approximately 1 cm above the carina and confirmed by using auscultation of breath sounds. The position of the tip relative to carina and site of prior TEF repair (if present) is confirmed using a fiber-optic bronchoscope (FOB) via the ET tube. The ET tube is then secured at the right side of the mouth with a "saliva-proof" taping technique.

Intraoperative airway obstruction may occur in these patients and is usually due to occlusion of the central airways by secretions and/or blood clots from local or pulmonary hemorrhage related to prolonged retraction. The first indication that this problem is developing may be a rise in peak airway pressure during positive pressure ventilation. Vigorous tracheal normal saline lavage and suctioning with Ambu® bag ventilation can be a lifesaving maneuver in this situation. A FOB may also be needed to dislodge clots and insure that the ET tube tip has not migrated past the carina or into a tracheal diverticulum (prior TEF). Tracheomalacia with long-term secretion clearance difficulties and subsequent bronchospasm are also frequently encountered and may respond to intermittent bronchodilator administration. If the patient comes to the operating room with a tracheostomy tube in place, it is usually changed to an oral ET tube for the procedure and changed back to an identical clean tracheostomy tube prior to transport to the PICU.

Volume-controlled mechanical ventilation with a low-compliance breathing circuit is generally used intraoperatively. Inspiratory to expiratory time ratio is typically 1:2.5–1:3.5, to allow for avoidance of air trapping from bronchospasm and/or inspissated secretion ball-valve effect, especially in the "down lung." Positive end expiratory pressure (PEEP) is at 0–4 cm H_2O and FiO_2 adjusted to keep oximetric oxygen saturation ≥92 %. After the chest is closed, a PEEP level of 5–10 cm H_2O is used to restore functional residual capacity (FRC) in the PICU setting. Ventilation strategy at this point should transition to a style which reduces ventilator-associated lung injury (VALI).

Intraoperative Monitoring Capability

The anesthetic maintenance is principally a balanced inhalation technique with isoflurane, taking into account the patient's prior anesthetic experience, renal function, and chronic medication regimen. Those patients with extensive previous narcotic exposure are generally given 25–50 mcg per kg fentanyl during surgery. Fentanyl and midazolam infusions can be started prior to leaving the OR, helped with the administration of rectal acetaminophen and, occasionally, dexmedetomidine [20]. In addition, the thoracotomy incision is infiltrated with an appropriate dose of a long-acting local anesthetic such as bupivacaine or ropivacaine. Epidural analgesia is avoided at present since NM blockade is a regular feature of PICU care [21].

When CV shunts are present, extra care should be taken to avoid paradoxical air or particulate embolization [19]. Blood pressure instability is relatively common and may be due to a retraction-related mediastinal distortion, inadequate pulmonary gas exchange, possible sudden hemorrhage, or even septicemia. The desirability of monitoring right heart filling pressure, rapidly provide volume, and check blood gases make deep or central venous line placement necessary. At times, the upper body may not provide the best central venous line site, due to the presence of a cervical esophageal fistula with associated heavy bacterial skin colonization. In this situation, the common femoral vein can be used for low inferior vena cava access. Pre- and intraoperative ultrasound is especially useful for line placement because many patients will have had several lines previously placed. An arterial line is also recommended, particularly if the lower esophageal segment is very small, and considerable retraction of the liver and diaphragm will be necessary to get it on the correct path up into the right pleural space. The arterial line is usually removed after the first postoperative night.

Temperature monitoring is best accomplished at the nasopharyngeal (NP) site. A forced-air warming device and IV fluid warmer is always used for avoidance of extreme temperature swings. NP temperature is maintained in the 36–38° range. Subacute bacterial endocarditis (SBE) prophylaxis may be warranted and should be of an esophageal variety, irrespective of wound infection prophylaxis [18].

Care During Growth Period

The postoperative care of these patients is complex and sometimes quite protracted. The early phase of this care is directed at vital sign stabilization and recovery of pulmonary function. A chest radiograph is quickly obtained to verify correct tube placements and to rule out abnormal gas collections. Upper and lower pouch markers with Ligaclips are placed at the time of the first stage and must be identified with the surgeon on the post-op film as well as the "stop markers" placed on the posterior thoracic wall to signify the extent of the available space in which to advance the pouches. The upper right lung field will commonly reveal changes consistent with pulmonary contusion and accompanying atelectasis.

The PEEP level is then set to allow for alveolar recruitment, with tidal volume (6–8 cc/kg effective) and peak positive airway pressure adjusted ($\leq$35 cm H_2O) to minimize the chance of significant VALI. Aspects of preoperative respiratory care such as chest physiotherapy and bronchodilator therapy are then resumed and perhaps intensified as needed. Also, whenever possible, the patient should be nursed in the $\geq$30° semierect position. Prone positioning has been undertaken with great success in recruiting alveoli.

A daily CXR is used to follow FRC maintenance, proper tube position(s), contusion evolution, and atelectasis or pneumonia development as well as gap length. If the markers appear further apart on CXR or the sutures have pulled free, the surgeon needs to be notified and an esophagram should be performed to identify if an esophageal pouch has pulled free of its traction mechanism. If the pouch has pulled free, the child should be taken back to the operating room to replace traction sutures in a timely manner (24–48 h) to avoid losing the length that has been gained. In addition, recalcitrant lung field opacities on CXR should be investigated with FOB and bronchoalveolar lavage (BAL), for early and aggressive treatment of nosocomial pneumonia.

There should be no vigorous diaphragm movement, especially "hiccups," during the time the esophageal ends are on increasing traction or for 3 days following fixed or internal traction. In order to facilitate this, we routinely employ paralyzing agents such as vecuronium. NM blockade has been continued for as long as 1 month, especially when staged repair with traction sutures is the chosen surgical strategy. A continuous dosing strategy that avoids complete paralysis with daily NM blocker "holidays" is useful to ensure neurologic integrity and lessens the chances of long-term PICU neuromuscular syndrome [22, 23]. Although it is possible to only use paralytics to prevent violent diaphragm movement such as coughing, vigorous crying or hiccups, we have found that it is difficult for the nursing staff to allow for wiggling of fingers and toes and yet prevent potentially detrimental movement. Nevertheless, this should be the goal.

The addition of narcotics and antianxiolytics to this regimen is necessary for the child's comfort and dependence is inevitable. Frequent dexmedetomidine holidays may be helpful in reducing the total accumulative dose, and whenever possible, short-acting agents should be transitioned to methadone and Ativan for long-term control and weaning [24]. Withdrawal scales are routinely employed and are helpful in developing a weaning plan for each child. Following subsequent surgical procedures, additional pain management is provided in excess of baseline medications and used for the duration of acute pain.

Significant perioperative cardiac care is commonly required. Inotropic support may be necessary during acute inflammatory stages but is rarely needed for the long term or at a high dose. Occasionally, there may be evidence of myocardial irritation in the OR during aggressive

retraction, but this generally resolves with adjusting the force of retraction. Central lines placed in the OR are removed as soon as possible in the postoperative period, and ventilator support is managed with the use of VBGs and end-tidal CO_2 monitoring. Central venous lines are exchanged for long-term peripherally inserted central catheter (PICC) lines placed on the right side ideally to prevent thrombus formation in the innominate vein, thus predisposing the child to chylous effusion [2].

The Growth Period and Postoperative Care

Gastric feedings are avoided, while the lower pouch is on traction because of the possibility of esophageal perforation and leak and the common gastroparesis/delayed emptying and subsequent reflux present when the patient is on high-dose narcotics/benzodiazepams and paralytics. If a gastrojejunostomy (GJ) tube is in place, feeding may be provided either as trophic support or full enteral support if tolerated. If parental nutrition is required, particular care must be given to ensure that optimal nutritional support is provided. The actual measured energy expenditure of these infants while sedated and ventilated may be as low as 50 % of what would be expected if they were healthy and normally active [25, 26]. The glucose infusion rate (GIR) goal is typically 7–9 mg/kg/min while paralyzed and increased to 10–12 mg/kg/min when extubated with adjustments made when there is evidence of high CO_2 production from over feeding. Amino acid (AA) goals for infants are 2.5–3 g/kg/day and intralipid (IL) goals are 3 g/kg/day. Based on adult studies, glutamine-supplemented TPN may be beneficial starting at 0.1 mg/kg/day and advancing to 0.3 mg/kg/day in the absence of renal failure or metabolic disorders. Levocarnitine may be added to shuttle the fatty acids into the mitochondria. Low-dose heparin is routinely added to prevent thrombus formation in the inactive child.

Close attention must be provided to ensure a calcium phosphorous ratio of 1.3:1 to help prevent osteoporosis in the inactive infant on paralytics and heparin. Nutritional supplements with calcitriol or Fosamax may be necessary if there is early evidence of osteoporosis and clinicians should work closely with radiology, clinical nutrition, and pharmacy to identify early evidence of derangements including fractures. It is important to ensure all requirements to maintain bone structure are being met [27, 38]. Range of motion (ROM) exercises are beneficial to boney structure and should be done at least once a shift by the nursing staff.

As mentioned above, the child should be nursed with the head of the bed (HOB) elevated at least 30° to facilitate secretion clearance. When suctioning the oropharynx, it is essential that the child not be suctioned too deeply. The measurement from the tip of the nose to the ear to just above the clavicle should be recorded and suctioning limited to this distance to avoid perforation of the upper pouch. If necessary, a small sump or Replogle tube can be placed in the upper pouch proximal to the end and placed to low intermittent suction if there is concern for chronic aspiration and airway soiling [7, 28].

When not being fed, the gastric tube should be left open to air to allow for decompression. Gastric pH is strictly maintained between 5 and 7 with the aid of intravenous (IV) H_2 blockers and/or PPIs. While the lower pouch is on tension potentially distorting the lower gastroesophageal junction, it is presumed that there is free reflux, and any acid exposure of the lower pouch may produce erosion and ultimately perforation [29–31]. Continued vigilance at medically managing reflux (which has been well described in the literature) is maintained until surgical management can be achieved. Most commonly here, around 2–3 weeks postprimary repair, a fundoplication is done for significant reflux. Reflux treatment is continued for several months after Nissen fundoplication until esophagoscopy and biopsy reveal no esophagitis is present. While the patient is NPO, routine Maalox and Carafate use is avoided because of the concern for bezoars formation [32]. G-tube medication in general is avoided, as there is the potential that anything put in the stomach could end up in the pleural space, via lower esophageal pouch leak, especially if it is

given in large volumes or with great force. Any medications deemed necessary to be delivered in the stomach while the lower pouch is on tension must be given gingerly, and the G-tube should be open and elevated following administration rather than clamped.

Chest tubes are routinely placed in the OR following each thoracotomy and are typically held away from the esophageal pouch/anastomosis with a retention suture placed on the lateral thoracic wall to prevent esophageal damage as a result of direct contact with suction from the Pleur-evac or stripping of the chest tube. During the growth stage, the chest tubes can safely be removed on postoperative day 2–3 if no air leak is present and drainage is minimal. At the time of the primary repair, it is advisable to leave the final chest tube in place until the child is awake and swallowing secretions as evidenced by G-tube drainage. No saliva should be seen in the chest tube to ensure no significant esophageal leak is present prior to removing the chest tube.

Intensive physical therapy is initiated as soon as the child stabilizes after the operation. Full passive ROM exercises are provided on a daily basis paying particular attention to the right arm to prevent adhesions of the scapula and a frozen shoulder. As soon as the child is off paralytics, resistance therapies are provided to help prevent osteoporosis. Once the child is extubated, speech and occupational therapy (OT) is initiated and provided on a daily basis to begin oral stimulation and facilitate transition to oral feeds. Feeding therapy may be a long-term task because eating and the act of purposeful swallowing itself is foreign for these infants and must be learned. This lack of understanding of the need to eat may produce an oral aversion [2, 11, 15, 31, 33–37]. A dedicated speech therapy/OT team is critical to long-term success and will follow these patients throughout their hospital stay and as an outpatient to support normal eating habits. These therapists may detect early strictures and are central to helping the family learn healthy habits.

Infectious issues may also be significant in the perioperative period and range from blood stream infections (BSAs) to ventilator-associated pneumonias (VAP) and empyema. Routine prophylactic antibiotics are generally only provided for the first few postoperative days and then discontinued while strict preventative maneuvers are undertaken to avoid BSA and VAP. If an esophageal leak is present, appropriate antibiotics and antifungals are provided based on culture and sensitivities. In many cases, a small contained leak can be treated with placement of a chest tube near the site to allow drainage of the fluid and promote sealing of the hole. Once the leak has sealed, the chest tube is backed out slowly about a centimeter a time over the course of a week or 2 to allow proximal healing and adhesion formation.

The Effects of Near Paralysis

Long-term immobility and postsurgical inflammation/cytokine release produces fluid overload and edema. Keeping the serum albumin level in the high normal range can help maintain intravascular volume by the oncotic pressure despite the leakage that occurs. These patients, however, will typically also require long-term diuretic therapy, which, although necessary, has risks and must be monitored. Prolonged loop diuretic therapy can result in chronic hypercalciuria, which predisposes to nephrolithiasis, renal calcifications such as staghorn calculi and nephrocalcinosis, and bone mineral depletion [38]. As discussed earlier, one of the problems for these patients is osteoporosis and diuretic therapy adds to the risk. Electrolytes must be carefully replaced and frequent monitoring of serum levels is essential as is early recognition of renal stone formation with ultrasound. Neonates in whom furosemide has been combined with prolonged total parenteral nutrition may also develop gallstones [38]. Any child on long-term or high-dose diuretics such as furosemide is also at risk for hearing loss. The consequences of diuretic therapy are now better understood and hearing loss avoided; nevertheless, hearing screens may be warranted if concerns arise.

Comprehensive social support is frequently overlooked with these children and families. Often times, a family travels a great distance to

arrive at a program specializing in long-gap repair, and they have left behind financial security and their emotional support systems. Early intervention with social services may provide financial and emotional support as well as help families cope with this difficult time period. Meeting with the family for an extensive discussion of the various stages and the anticipated hospital course is beneficial.

It has also been valuable to identify the times frequently associated with the greatest potential for frustration. These include dealing with oversedation vs. withdrawal, with slow progress in feeding, and with leaks and strictures. Often the families find it helpful to have written information of the various stages and radiographic studies as well as target care issues.

Explanation must be provided that each child is different and the surgical approach and time frames are rough estimates and their child may progress to the next stage more rapidly or may take much longer. Routine updates as to patient progress and the next goal will benefit both the family and the care providers. Allowing time for questions and expression of concerns is essential.

Finally, the importance of a team approach cannot be overemphasized. Daily review of the studies and pertinent data with the key providers is crucial with frequent whole team discussions. As each child's anatomy and response to growth is unique, viewing the patient from all angles by all providers is the best way to develop a plan that fits each child best and has the greatest chance of complete success.

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27 The Growth Potential (Form and Function): The International Esophageal Growth Experience

Khalid M. Khan

Introduction

Growth and development are the biological processes that lead to maturation of living organisms. Tissue growth is a regenerative response to injury although not in all organ systems and not as part of all types of injury or defect. Some organ systems have immense regenerative capacity such as the liver after resection, while ischemic injury of the heart and brain by disease are followed by replacement with significant scarring. In the alimentary tract, the small bowel is well known to have the ability to adapt to shortening by disease or resection especially in infants. It does this by increasing the surface area through luminal dilation and altering mucosal structure to improve absorption. The finding that the response is related to glucagon-like polypeptide (GLP)-1 has led to the development of a specific treatment for short bowel syndrome by enhancing this effect [1]. To an extent, the natural growth potential noted in other tissues has also been demonstrated for esophageal pouches in patients with long-gap esophageal atresia (LGEA) in the first few months after birth [2]. To restore the esophagus, i.e., form and function in patients with LGEA, enhancing this growth potential would be a way to bring the two esophageal pouches close enough to each other for primary repair to be accomplished.

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The Esophageal Response to Traction

Traction as a method of esophageal growth has been primarily developed by Dr. J.E. Foker at the University of Minnesota with a unique procedure developed over two decades ago (see Chap. 45 for a detailed discussion of the procedure). The aim was to bridge EA gaps that were long (>2.5 cm, <3.5 cm) or ultra-long (>3.5 cm) at birth. In the case of ultra-long EA surgery to elongate the esophagus or an interpositional graft would otherwise be necessary [3]. Beyond the notion that the esophagus is the best conduit to the stomach, he sought to take advantage of the natural potential for growth in children and determined that tension would be a stimulus for growth of the esophageal pouches. This assumption was not without precedence as over three decades ago Puri et al. showed that primary delayed closure was a possible method to manage some cases of LGEA [2]. The presumed stimulus for the natural growth of the upper pouch was the swallowing reflex and for the lower pouch the stimulus was reflux of gastric

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contents. It was noted that the maximal natural growth of the esophageal segments occurred during the first 8–12 weeks of life, and it led the investigators to purpose that the ideal time for delayed primary closure of EA was when the infant reached approximately 12 weeks of age [2]. The traction procedure as proposed by Foker was therefore as an extension of primary delayed closure; applying traction to the end of the pouch would simply enhance the natural tendency of the pouches to elongate. Other methodologies with a similar premise including daily bougienage of the proximal esophageal pouch during the waiting period and the use of high-volume bolus feeding through the gastrostomy in the hope that gastroesophageal reflux will occur and result in stretching of the distal esophageal segment have not been demonstrated to be effective [4]. The major drawback to the principle of delayed closure is the time period involved and the possibility of respiratory complications. Furthermore, ultra-long gaps with a very small lower esophageal pouch cannot be adequately developed to be able to bridge the gap simply by waiting.

The esophagus is a highly elastic viscus that normally retracts when transected and in the type A or pure EA where there is no lower pouch fistula to the trachea the pouch itself maybe very small and retracted in appearance. While there is likely some recoil in the lower pouch, the extremely small pouch clearly lacks mass (Fig. 27.1) and therefore real growth has to occur for it to be anastomosed. The integrity of the very small lower esophageal pouch for an attempt at primary repair of LGEA has always been questioned. At the University of Minnesota, it was previously shown that the anatomic structure and in particular the muscle layers are well preserved after traction has resulted in elongation of the lower and upper pouches including the overall luminal thickness [5, 6]. And despite the initial size of the pouch, the physical appearance and indeed the feel of the viscus are astonishingly normal even after significant lengthening following traction (Figs. 27.2 and 27.3). Of note, traction applied to the small bowel in an animal model was shown to result in growth of the small bowel as measured by tissue components including protein content and the bowel appeared morphologically normal [7]. The rate of growth of the small bowel in this study was similar to that achieved with esophageal trac-

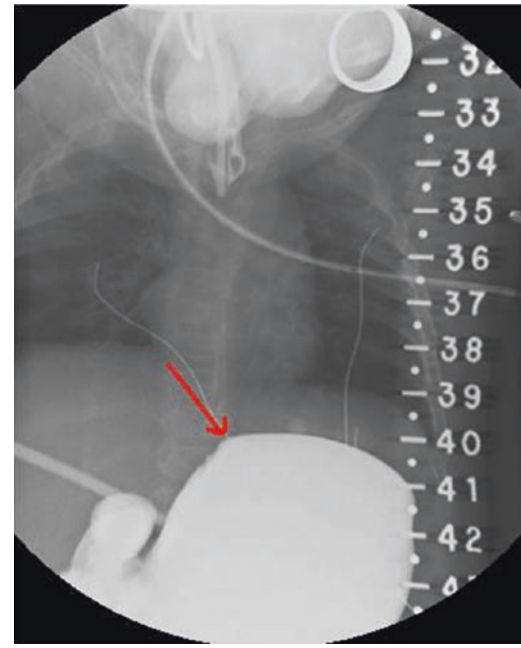

Fig. 27.1 Radiograph showing a miniscule lower esophageal pouch

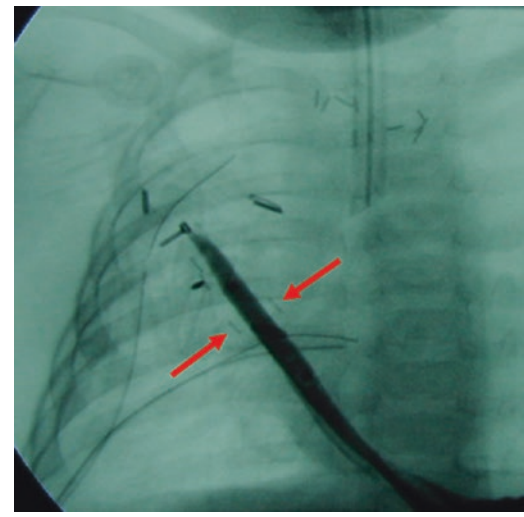

Fig. 27.2 An intraoperative field showing the esophageal form after traction

tion described in the Foker technique [5, 6]. An estimation of the rates of growth and lengthening of the esophagus and what is tolerable by the esophagus was a principle learned throughout the development of the technique by Foker [3, 8]. The estimate of growth of the esophageal segments in the series averaged between two and three times the original length, and this was accomplished within 2 weeks and up to 4 weeks (Fig. 27.4) [9, 10].

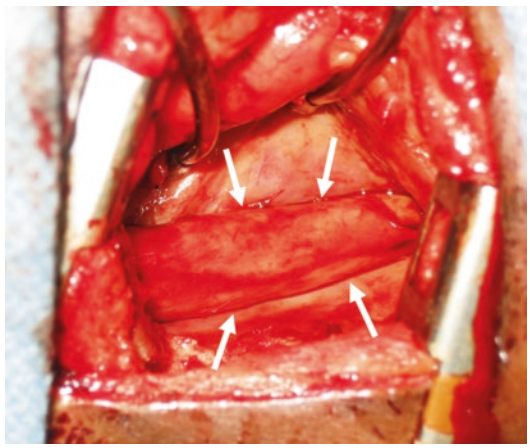

Fig. 27.3 An intraoperative field showing the esophageal form after traction

International Experience with the Growth Procedure

As with any new and novel technique, there have to be periods of assimilation and investigation by others as to the validity and feasibility of such an enterprise. There are some natural boundaries to this. While EA with tracheoesophageal fistula (TEF) presents frequently enough to pediatric surgeons for them to develop familiarity with the logistics of primary repair, LGEA is a relatively uncommon condition even for pediatric surgeons [11]. In its different forms, LGEA represents a challenge, and most pediatric surgeons will have their own algorithm for dealing with the complexities that include managing comorbidities that constitute the various syndromes associated with EA.

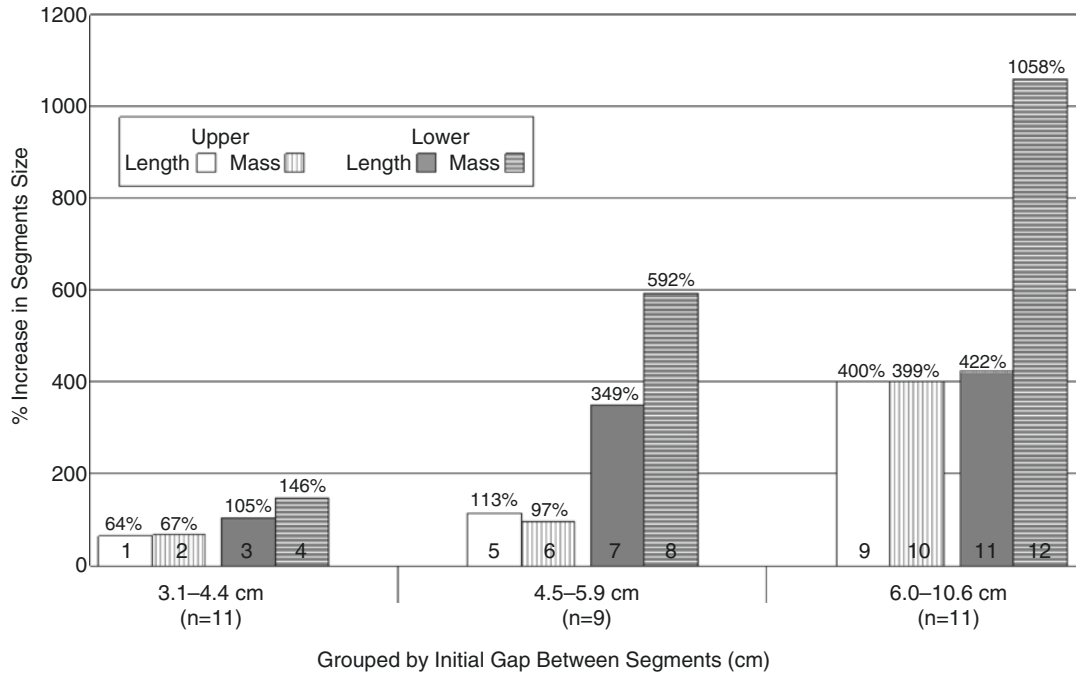

Fig. 27.4 Tension induced growth in upper and lower esophageal segments

The Algorithm for Long-Gap Esophageal Atresia Repair

Where radiological measurement of the esophageal gap has been supportive enough for delayed primary repair, the initial decision to wait is a reasonable consideration. Similarly the subsequent confirmation that the pouches can be approximated is also a decision that would be made without great deliberation though there is no certainty that primary anastomosis will be possible in the operative filed. It has been proposed by Foker that this is the ideal stage at which traction should be considered, i.e., when it is clear that a primary repair cannot be concluded [10]. The intuitive surgery for the truly long gap at this time is to acknowledge that the extremely short lower pouch is not useful and proceed to non-esophageal options. The gastric cavity is therefore either fashioned in to a conduit or bypassed by an intestinal component. In a survey of 88 pediatric surgeons from various countries, it was noted that the preferred method of bridging large gaps is with part or entire gastric cavity [11]. In the same survey, it was noted that approximately 40 % of surgeons would attempt the Foker procedure, and this was consistent in a follow-up survey [12]. These figures would suggest that in the case of the miniscule lower esophageal pouch, there is likely conviction in a significant proportion of surgeons that even the Foker procedure would be able to facilitate a primary repair.

Physiology of the Growth Procedure

Although it is not difficult to imagine normal physiological growth in early life, there is perhaps resistance to the concept as a treatment method and the notion that true growth can occur as part of the reparative process. In this debate, an appropriate response would be that regrowth involving limbs is a known phenomenon in some organisms, and as noted above, there is evidence to support the premise that functional growth can be stimulated even in the human alimentary tract. The success of tissue distraction most clearly for the skin and bone is testament to the concept that tension is a normal stimulus for growth in other organ systems. While it might be argued that to apply the principle of traction to growth of a complex structure such as a viscus may interfere with or cause derangement of function, the primary function of the esophagus is as a conduit to the stomach, and this is clearly achieved with primary repair of LGEA. Furthermore, in the case of EA, reestablishing esophageal continuity allows the stomach to be used for its proper purpose rather than being cannibalized to fashion a conduit. And normal esophagogastric function not only has implications for pathophysiological well-being but also for psychosocial development and later a normal relationship to food [13]. Further support for the concept of growth comes from the field of tissue regeneration, including the use of stem cells, an area that has developed in to a specialty in its own right [14]. Similarly to the use of traction this area of therapeutics is based on the premise that the natural process of growth can be reproduced for repair of tissue and organ systems (see chapter on tissue regeneration and stem cells).

A particular concern in regard to the principle of growth through traction has been the frailty of the lower esophageal segment in type A esophageal atresia when there is only a miniscule lower segment (Fig. 27.1). Overstretching of the esophageal muscle could potentially lead to fiber damage, and excessive mobilization of the very small lower segment may result in ischemic damage. There are however reports noting that the inferior segment of the esophagus can be mobilized without fear of provoking ischemic necrosis and that this results from the fact that the distal esophagus does not receive its blood supply from the thoracic aorta, as it has been thought, rather the supply is from the phrenic arteries or the proximal gastric collaterals [15].

Technical Aspects of the Foker Procedure and "Thoughtful Persistence"

In an international survey of pediatric surgeons, a proportion of those who attempted the Foker technique (24%) were not satisfied with it [11]. As noted above, successfully performing a surgical procedure such as the Foker technique with all of the nuances will involve a learning curve, and in the above survey, individual surgeons managed <2 cases/year. In describing the first use of the Foker technique for a case of an ultra-long-gap EA performed at their institution by Paya et al., the clinical course of the child was "surprisingly uneventful" [16]. Compared to other procedures, the authors reported that the complication rate was acceptable and primarily related to their lack of experience with the new method. It has to be noted therefore that with the relatively few cases of truly LGEA, the failure rate in performing the growth procedure may remain high in part related to the paucity of experience of individual surgeons.

The most specific intraoperative issue that has been discussed is the potential for traction sutures to detach and the possibility of mediastinitis, especially if esophageal perforation occurs [17]. Although the use of pledgeted sutures should minimize shearing forces at the tissue level, these sutures have been noted to cut through [18]. Al-Qahtani et al. in their discussion of pledgeted sutures cutting through suggested that the optimal size, quantity, material, and placement technique for the traction sutures has yet to be determined [19]. In a case series, Abraham et al. used purse string sutures and found that they did not slip as compared with their experience with single sutures [17]. The authors indicated that in their opinion sutures slippage was one of the reasons preventing the widespread acceptance of the growth procedure. This case is an illustration of how potential modulation of the technique by individuals within their own circumstance is possible if there is resolve to achieve primary repair. One can therefore postulate that a reason for lack of success is resorting to alternative methodologies rather than thoughtful persistence. Of course the reason to persist in trying to achieve a primary repair would be a conviction on the part of the surgeon that the patient would be better off with his/her own esophagus in place and that this end justifies persistence on the part of the physician and parents. Other reports have also commented on the effect of tension on the extracorporeal sutures and recognizing the suture rupture early on as an important potential technical problem [16]. The authors in this report determined that "such a rupture could be depicted better by placing the clips on the end of the esophageal pouch rather than across the sutures" and that if rupture occurs, applying new traction sutures would be better than forced anastomosis under tension.

The most significant potential early postoperative complication of a primary anastomosis under tension is an anastomotic leak. In a report by Burjonrappa et al. of two infants among 15 with LGEA who underwent the growth procedure, one anastomosis performed at 18 days of life was complicated by an anastomotic leak that healed spontaneously [20]. Unfortunately, the subsequent course was complicated by an esophageal diverticulum that was not salvageable and led to an esophagogastric dissociative procedure in the end. This case clearly serves to highlight the complex issues that may be faced in this patient group and that there will be cases that defy even the most obvious and routine treatments. It has to be borne in mind that these instances do not necessarily determine a change in approach to all cases but rather to acknowledge the particularly challenging ones.

As noted earlier, predetermined ideas about what may or may not be possible in any given clinical circumstance determines the approach taken, and the natural instinct for LGEA is that a primary repair will be impossible. It has been discussed that to accomplish a primary esophageal repair with a particularly long gap of 5 cm or greater, usually it would be necessary to pull up part of the stomach up through the esophageal hiatus and that this maneuver, however, may lead to severe continuing reflux, so that most surgeons would choose to replace the missing esophagus

with a gastric or colon interposition [21]. Gastroesophageal reflux following primary LGEA repair is the most significant problems faced by physicians caring for these patients both in the short and long term. It can be agreed upon that the short-term surgical solution is predicated on the concern that the gastroesophageal junction is naturally displaced upward with traction and that free reflux would further complicate any anastomotic leak, the possibility of stricture formation, and respiratory complications. The most suitable surgical procedure to deal with a displaced gastroesophageal junction is debated but having a dysmotile lower esophagus implies that a tight fundoplication may be counterproductive [22]. Indeed it can be argued that the most important consideration is having the gastroesophageal junction below the diaphragm. The limited data on the long-term outcome does indicate that a fundoplication will be necessary after primary repair of LGEA and that even after a fundoplication reflux may be an issue and requires follow-up [23].

Drawbacks to the growth procedure have been argued to be the need for repeated surgeries, including thoracotomies, the high incidence of postoperative gastroesophageal reflux requiring fundoplication, and a high risk of stricture formation dedicating the patients to a prolonged series of repeated esophageal dilations [24]. Despite all these possibilities, the outcome may justify the use of the growth procedure. For instance, in a case discussed by the editors (H Till and JE Foker) where an anastomotic stricture developed following traction and gastroesophageal reflux was evident, dilations were effective in relieving the stricture and a fundoplication successfully controlled the reflux [24]. Although the entire event required three operative procedures and the patient was hospitalized for 2 months, the outcome was deemed to be "very acceptable," given that an esophagus-only repair was achieved with the gastroesophageal junction below the diaphragm and the authors postulated that the "benefits of the repair should only increase with time." Similarly other authors have described how challenging EA repair was successfully brought to an acceptable conclusion eventually with the use of the growth technique [25]. By way of contrast in a series of gastric transposition, anastomotic leaks and strictures were not uncommon by report [26]. In the overall analysis, it has to be acknowledged that management of the LGEA using traction to enable primary repair is not a singular event but a process that extends from initial assessment until a functional esophagus has been completed and this entails assembling a suitable team of physicians and related staff who then would develop a specific expertise in treating LGEA. It goes without saying that problems may be faced at any stage of the process and there has to be a resolve to work through these. Regardless of whether there is a lengthening procedure or transposition to manage LGEA, it is now clear that these patients will require long-term follow-up.

Summary

The procedure of inducing growth of the esophageal pouches by traction to enable primary repair of LGEA is acknowledged to be a relevantly recent innovation [10]. Despite this, it was the second most commonly performed technique for LGEA among international surgeons surveyed (76%) [10]. There is also no doubt that surgeons have found challenges when applying the technique and have not always achieved success. It can be argued that the alternative, that is, to replace the esophagus though not an easy option, intellectually makes great sense from a practical standpoint at the time of the surgery. The challenging nature of the growth induction method cannot be denied; however, the ultimate aim if achieved is far more acceptable for patients than replacement of the esophagus. It remains to be seen as to the resolve of physicians in achieving this goal.

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Part VII

Interposition Grafts to Establish Continuity

Gastric Transposition in Infants and Children

28

Robert A. Cowles and Arnold G. Coran

Introduction

The importance of an intact and functional esophagus cannot be overemphasized. Congenital and acquired diseases of the esophagus have significant adverse effects on growth and development. Conditions such as esophageal atresia with tracheoesophageal fistula can usually be adequately treated with direct surgical techniques, and these have been shown to result in excellent long-term outcomes. In other children, however, such as those with complex long-gap esophageal atresia and those with severe corrosive esophageal injury due to caustic ingestion, an excellent outcome cannot be guaranteed via the standard surgical approach. In these cases, replacement of the esophagus with a conduit may be the only viable alternative in order to restore anatomic and functional continuity between the mouth and the gastrointestinal tract. It is generally accepted that the ideal esophageal replacement conduit for children should (a) be long-lasting, (b) be associated with minimal reflux, (c) be technically feasible, (d) not affect cardiac or pulmonary function, and (e) allow oral consumption of nutrition. While the colon interposition and gastric transposition are the most commonly applied esophageal replacement procedures, other techniques have been described (Table 28.1) and can be considered under certain circumstances. This report will review the experience with gastric transposition procedures for esophageal replacement in infants and children.

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History

The concept of using a gastric conduit for esophageal replacement was developed while treating adult patients with esophageal cancer. These procedures involved a combined abdominal and cervical approach with eventual cervical esophagogastric anastomosis. When compared to transthoracic esophagectomy, this approach resulted in no thoracic incision and left the anastomosis in the neck, where a leak, if it occurred, would be

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more easily managed. The use of this procedure in children is limited mostly to treatment of benign processes and has gained increasing support.

Indications

Indications for esophageal replacement are varied (Table 28.2). In the pediatric population, the majority of cases involve esophageal atresia with long gap or patients who failed primary esophageal repair. When a primary anastomosis is impossible due to the distance between the two esophageal pouches, an esophageal replacement procedure should be considered. Whether a cervical esophagostomy is performed or not is a matter of surgeon preference. Children can be effectively managed with nasoesophageal suction temporarily while awaiting a definitive procedure. If the delay prior to definitive repair is predicted to be lengthy, however, a cervical esophagostomy may allow for sham feeding and care at home without fear of aspiration.

Caustic ingestion injuries to the esophagus remain an important indication for esophageal replacement. This indication is more commonly seen in developing countries, where caustic agents are an ongoing cause of injury due to poor packaging and care of these agents. While some caustic injuries are treated with dilation and supportive measures, severe injuries may not respond and replacement can be considered. Severe, unresponsive peptic strictures, tumors, and inflammatory conditions are uncommon indications for esophageal replacement [1].

Table 28.1 Types of esophageal replacement procedures

Colon interposition
Gastric tube (antiperistaltic and isoperistaltic) – Gavriliu
Jejunal interposition
Gastric transposition

Table 28.2 Indications for gastric transposition

Isolated esophageal atresia with long gap
Failure of alternate esophageal conduit
Failure of standard repair of esophageal atresia
Caustic ingestion with persistent stricture
Persistent peptic stricture
Tumors (diffuse leiomyomatosis, inflammatory pseudotumor)
Foreign body injury (e.g., battery)
Achalasia

Timing of Surgery

Esophageal replacement is an elective operation and should not normally be considered in an urgent or emergent setting. The timing of esophageal replacement depends primarily upon the underlying condition leading to replacement surgery. In cases of caustic ingestion with persistent stricture, surgery is often considered once standard therapy consisting of serial dilations has failed, usually after 6–12 months. The timing of surgery in infants with esophageal atresia, however, is more variable. Traditionally, a feeding gastrostomy is inserted once the diagnosis of long-gap esophageal atresia is made. Some advocate a cervical esophagostomy to allow sham feedings and safe discharge home without suction or before eventual transfer to a facility for definitive care. Alternatively, a sump suction tube can be left in the pouch for drainage of oral secretions until a definitive repair can be performed. Often the final decision to perform a definitive esophageal replacement is made once other options have failed or if the gap between the ends of the esophagus is deemed far too great to even attempt primary repair. This determination can be made after about 3 months of age. When considering gastric transposition in the setting of long-gap esophageal atresia, enough time must be allowed for adequate growth of the stomach as an adequate conduit will need to reach the region of the left neck.

Preoperative Preparation

Preoperative evaluation of children who are being prepared for gastric transposition should be

geared toward the underlying condition. In cases of esophageal atresia, a cardiac evaluation, pulmonary functional assessment, and a reliable measurement of gap length should be performed. In the setting of caustic ingestion, pulmonary function and the quality of the stomach should be assessed. An endoscopy, if possible, will delineate the stomach, and an assessment can be made of its usefulness as a potential conduit. We recommend a formal bowel preparation in the event that the stomach is not usable and an alternative conduit is contemplated. If possible, an evaluation of vocal cord movement is advisable preoperatively in all cases to document the status of the recurrent laryngeal nerves before surgical manipulation of the neck.

Technical Details of Gastric Transposition

The patient is placed supine on the operating table, generally with the left chest elevated and the left arm prepped and mobile in the field. This allows for exposure of the left neck. The IV lines should be placed in the lower extremities. In this manner, the neck, chest, abdomen, and left upper extremity are prepped and draped. The abdominal incision is made first. A gastrostomy is often present and should be taken down from the abdominal wall. The stomach should be freed from adhesions and, if present, a fundoplication should be unwrapped. The gastrocolic omentum with the short gastric vessels should be carefully divided as should the gastrohepatic omentum. The right gastric vascular arcade is preserved and the left gastric vessels are divided.

The distal esophageal remnant is then dissected from the mediastinum (Fig. 28.1a). In isolated esophageal atresia, this is often seen as a short diverticulum, which is easily dissected (Fig. 28.1a), but in cases of corrosive injury, the scarred esophagus is often difficult to dissect from the mediastinum. The gastroesophageal junction can be divided with a stapler or amputated and closed with sutures. The gastrostomy site can be removed similarly. These maneuvers free the stomach completely, preserving the blood supply via the right gastric artery and right gastroepiploic vessels (Fig. 28.1b).

By definition, the vagus nerves are divided bilaterally during the gastric transposition procedure, and most authors recommend either a pyloroplasty or a pyloromyotomy. Our group has used the pyloromyotomy with excellent success, and we feel that a formal Heineke-Mikulicz pyloroplasty is placed under tension when the conduit is pulled into the neck. It should be noted that the performance of a pyloromyotomy on an essentially normal pylorus requires significant care in order to avoid violating the mucosa. If necessary, a Kocher maneuver may be performed in order to allow the conduit to reach the neck.

The esophageal hiatus is opened from the abdominal approach. With retraction of the left arm, a left cervical incision is made and the cervical esophagus, or the esophagostomy, is isolated. Care should be taken in this area to avoid injury to the recurrent laryngeal nerves. In isolated esophageal atresia, when no esophagus lies in the posterior mediastinum, a path can be created for the gastric conduit using blunt dissection from the abdominal and cervical approaches (Fig. 28.1c). When the native esophagus has been present, it can be dissected bluntly and the resulting path can be used for the conduit. A large chest tube (28–32 French) can be passed from the cervical incision into the abdomen via the posterior mediastinal path. On the abdominal side, the tube is sutured to the fundus of the gastric conduit, which is the highest point on the stomach, with care taken to avoid twisting of the conduit as it is pulled through the posterior mediastinum. Once the conduit is comfortably pulled to the level of the left cervical incision, we recommend anchoring the conduit to the sternocleidomastoid muscle's medial boarder laterally and the strap muscles medially. A gastrotomy is performed and the upper esophageal pouch is opened. The most distal part of the upper esophagus and the apex of the gastric conduit are connected with a single layer anastomosis using interrupted sutures (Fig. 28.1d). A transanastomotic nasogastric or orogastric tube is left in place for decompression of the gastric conduit and to be used for a postoperative contrast study. The cervical incision is

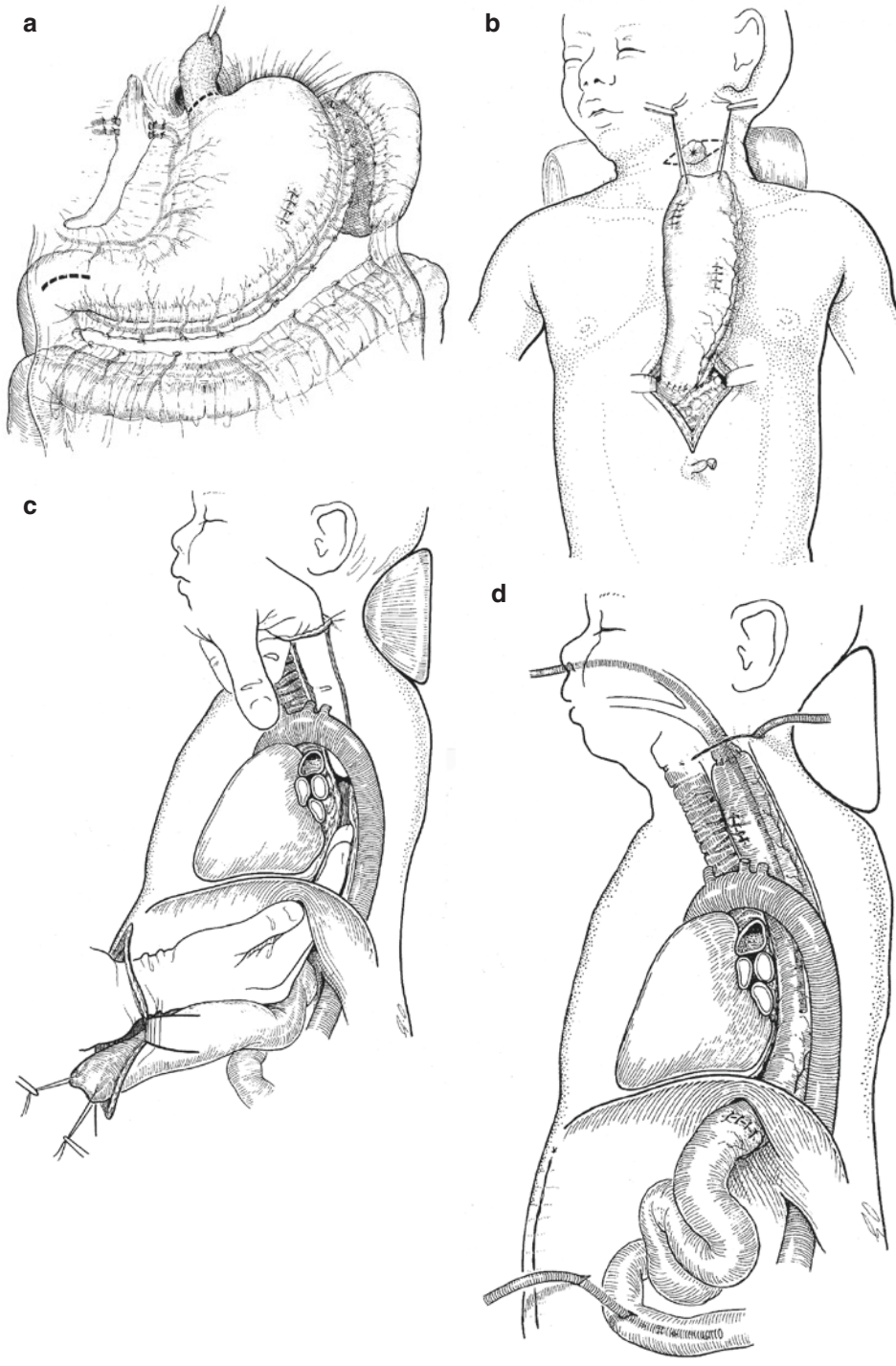

Fig. 28.1 (**a**–**d**) Technique of gastric transposition: (**a**) The stomach is dissected with care to preserve the right gastric and right gastroepiploic vessels. The distal esophagus is dissected from the mediastinum. In long-gap, isolated esophageal atresia, the distal esophagus is often a short diverticulum that comes off the stomach (shown). (**b**) The stomach is completely freed. The gastrostomy site and gastroesophageal junction are closed. Note the length that can be expected from the gastric conduit. (**c**) A posterior mediastinal tunnel can be created with blunt dissection. (**d**) The conduit is carefully passed via this tunnel and into the neck, where a cervical esophagogastrostomy is performed (Figures from Spitz [11] with permission)

closed over a Penrose drain. We obtain a contrast study of the conduit during the postoperative period to assess the anastomosis, evaluate for leak, and document gastric emptying (Fig. 28.2).

Postoperative feeding is achieved using a variety of methods. It should be stressed that the gastric conduit is aperistaltic and surgically denervated. For this reason, it must drain by gravity, making it imperative that these children feed orally in the upright position. Despite these maneuvers, however, many children have delayed oromotor function, and it is often difficult to fully nourish them orally immediately following gastric transposition. Nasogastric tube feedings can be employed but rely upon the security of a nasal tube. Alternatively, a feeding jejunostomy may be placed and used during the postoperative period. This latter approach must be considered in patients who have been fully reliant on their gastrostomy prior to esophageal replacement. Our preferred method is a "button-loop" jejunostomy rather than the standard Witzel tube jejunostomy. Briefly, the jejunum just distal to the ligament of Treitz is isolated, folded on itself, and anchored in a side-to-side configuration. The apex of the jejunum is opened, and an endoscopic stapler is used to create a side-to-side common opening between the two limbs. Two purse-string sutures are placed, and the tube is anchored once these sutures are tied and the tube is then brought through the skin (Fig. 28.3). The details of this technique have been previously published [2]. The technique allows for insertion of a replaceable button device that is secure, and the jejunostomy is not prone to obstruction. Another advantage is that when the jejunostomy is no longer needed, the button can be removed. Thus, this type of jejunostomy functions like a Roux-en-Y jejunostomy but is simple to perform and requires no operation to close.

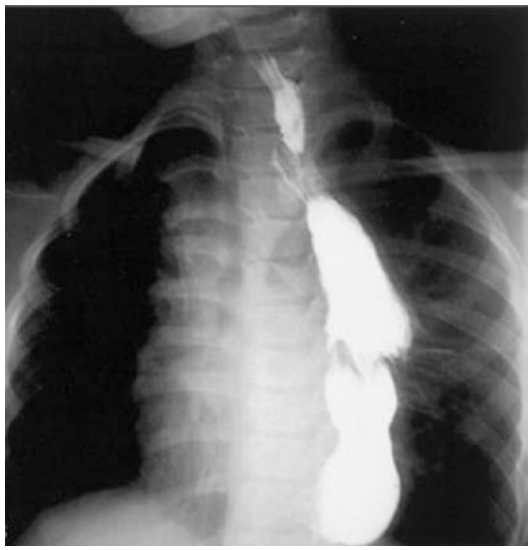

Fig. 28.2 A postoperative contrast study of the gastric conduit shows the stomach as a tubular structure in the posterior mediastinum (Figure reprinted with permission from [8])

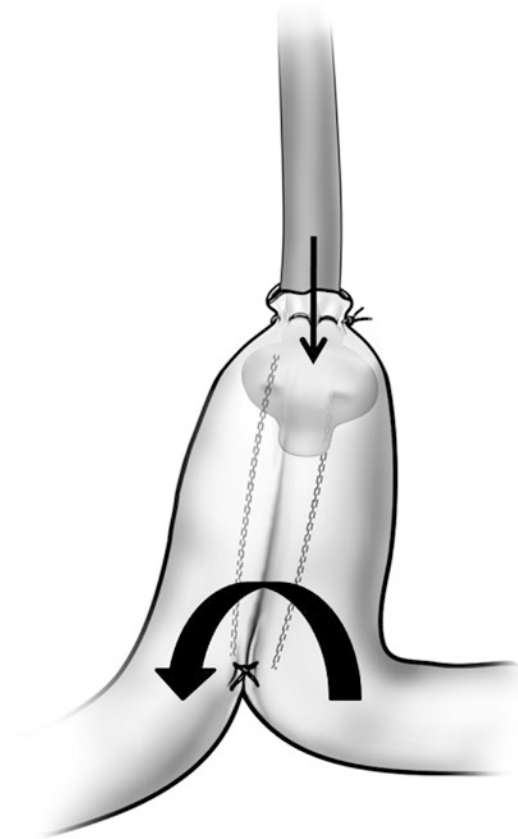

Fig. 28.3 Jejunostomy technique that creates a jejunal "loop" diverticulum. A replaceable balloon device can be used. Feedings are infused via the jejunostomy tube (*straight arrow*) and intestinal contents pass distally (*curved arrow*)

Outcomes

Few large studies exist that document outcomes of gastric transposition in infants and children. In 1948, Sweet published his description of gastric transposition which brought the stomach behind the hilum of the left lung and into the neck [3]. In 1984, Spitz reported his initial experience with four children with long-gap esophageal atresia where the gastric conduit was brought into the neck via the posterior mediastinum without thoracotomy in order to achieve a cervical esophagogastric anastomosis, an approach similar to what is often used in the treatment of esophageal cancer in adults [4]. Spitz published updates of his growing experience with gastric transposition in 1992, in 2004, and again in 2009 [5–7]. In the latest report, 192 cases were reviewed. Mortality rates were low (<5 %), but morbidity such as anastomotic leak (12 %), anastomotic stricture (19.6 %), swallowing dysfunction (30.6 %), and delayed gastric emptying (8.7 %) was not uncommon over the 25-year period [7]. Hirschl et al. reported a multi-institutional experience with gastric transposition in 2002 [8]. Of the 41 patients described, 26 had esophageal atresia. The mortality rate was zero and no conduits were lost. Interestingly, the reported rates for anastomotic leak (36 %) and stricture (49 %) were higher than those reported by Spitz. These differences are likely related to each group's definition of leak and stricture.

Davenport et al. reported long-term outcomes after gastric transposition in 17 patients who had undergone surgery more than 5 years previously [9]. In this study, gastric transposition was associated with diminished lung capacity, efficient gastric emptying, low iron stores, and overall excellent parental satisfaction. On average, children were also smaller than normal, but it is unclear whether this result is associated with the underlying condition or with the gastric transposition itself. In 2003, Ludman and Spitz reported on the quality of life of their gastric transposition patients [10]. Overall, nearly all patients reported high satisfaction and led a "normal" life after gastric transposition. There was a tendency toward social and emotional delays, and there appeared to be quality of life benefits for those who underwent primary gastric transposition versus those who had failed attempts at primary esophageal repair initially.

Since 1987, the senior author (AGC) has been involved in 169 cases of gastric transposition treated at several institutions, and, of these, 144 have adequate follow-up for analysis. In 111 (77 %), gastric transposition was performed for esophageal atresia, most commonly with long gap; 17 (12 %) for caustic stricture; 5 (3 %) for diffuse leiomyomatosis; and the remaining 11 (8 %) for failure of previous esophageal, tracheal, or upper gastrointestinal procedures. Currently, our approach is to perform the mediastinal esophageal dissection via a combined abdominal and cervical incision. No significant bleeding has been encountered as a complication. There are no postoperative deaths or loss of conduit in this series. One child developed cardiopulmonary arrest during a routine dilation procedure several months after a successful gastric transposition and suffered significant brain damage. This patient eventually died 1.5 years later from chronic renal failure. Another child with severe pulmonary insufficiency prior to the gastric transposition died 3 years after a successful gastric transposition from progressive respiratory failure. Another required takedown of a viable conduit due to persistent stricture at the esophagogastric anastomosis; this complication was felt to arise due to poor compliance with medication and follow-up. The relative rarity of major complications emphasizes the safety and efficacy of the operation.

Treatment Algorithm

Since most gastric transposition procedures are performed for long-gap or isolated esophageal atresia, the following algorithm has been adopted over the past 2 years by the senior author (AGC) when staging the care of these challenging patients:

1. The diagnosis of isolated (or long-gap) esophageal atresia should be confirmed, and the presence or absence of a proximal pouch fistula should be assessed via bronchoscopy or

during a careful contrast study of the upper pouch. A feeding gastrostomy is indicated early to facilitate feeding and to allow the stomach to grow and dilate.

2. At 6 weeks of age, the esophageal gap can be measured. The authors prefer a technique that uses a soft bougie in the upper pouch and a neonatal endoscope advanced via the mature gastrostomy site and into the lower pouch under direct vision (Fig. 28.4).
3. If the gap between the upper and lower pouches is three vertebral bodies or less, then a primary repair may be attempted. If the gap is greater than three vertebral bodies, then it is advisable to remeasure the gap after a second 6-week interval (a total of 12 weeks).
4. If the distal pouch resembles a small diverticulum or if primary repair appears impossible, a primary gastric transposition can be performed as described in this chapter at 12 weeks. If gap length suggests that primary end-to-end repair appears feasible, the child should be prepared for a right thoracotomy. The authors recommend patient positioning and an operative approach that would allow for conversion to a gastric transposition if primary repair turns out to be impossible. This requires that the abdomen, right chest, right upper extremity, and right neck be placed in the sterile operative field.
5. While wide dissection of the lower pouch is traditionally not recommended, taking down the diaphragmatic attachments to the esophagus, performing upper and lower pouch myotomies, and even ligating the left gastric vascular pedicle can facilitate a primary esophageal anastomosis. This approach has been used in five patients during this past year, with success in accomplishing a primary anastomosis in four. Only one of these five patients underwent a gastric transposition.

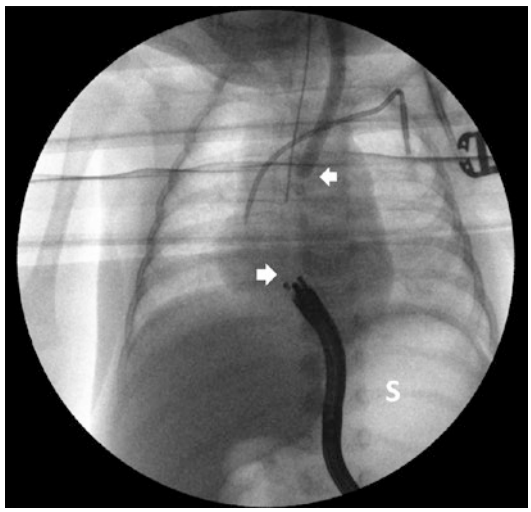

Fig. 28.4 Endoscopic technique to measure the gap between esophageal pouches in long-gap esophageal atresia. Placement of the endoscope into the stomach (*S*) via the gastrostomy ensures that the distal pouch is being clearly marked (*lower arrow*). A bougie dilator is placed from above to delineate the upper pouch (*upper arrow*). Fluoroscopic images are used to estimate the gap length

Conclusions

In children, esophageal substitution can be accomplished with a variety of intestinal conduits. Gastric transposition, while popularized for treatment of esophageal cancer in adults, is an effective esophageal replacement procedure. Gastric transposition obviates the need for a thoracotomy; places the conduit in the natural esophageal bed, preventing redundancy and lung compromise; requires only a single cervical anastomosis; and appears to be associated with excellent long-term outcome and patient satisfaction.

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The Gastric Tube

29

Gabriel O. Ionescu, Simona Gavrilescu, and Gabriel Aprodu

Introduction

"The best esophagus is the native esophagus" [1–3] is an almost universally accepted belief and has spawned a number of techniques designed to salvage the injured oesophagus or to permit an anastomosis where there is inadequate length in an atretic organ.

In developed countries, oesophageal replacement has become a rare operation in childhood, yet in developing countries, it is still frequently necessary in patients with extensive oesophageal injury due to caustic ingestion and in some cases of long-gap oesophageal atresia (EALG) [4]. Colonic graft [5–9], whole stomach transposition [10–13], gastric tube oesophageal replacement [14–18] and jejunal interposition [19–22] have all been used successfully, and selection of the procedure depends upon surgeon preference and experience as well as the anatomy of the injury. Recently, all of these procedures have been performed laparoscopically with promising results [23–27]. Other techniques for oesophageal replacement or reconstruction have been reported in small numbers including colonic patch [3, 28], sigmoid transposition with microvascular anastomosis [29] and different types of small bowel interposition [19, 21]. A few cases with isolated pedicled gastric tube graft and intrathoracic transposition have been also published [30–32]. Current research holds the prospect of oesophageal replacement using grafts created in the laboratory by tissue engineering techniques [33]. The long-term outcomes in adults following oesophageal replacement in childhood have been widely reported [34–37].

This chapter is devoted to the technique of gastric tube replacement of the oesophagus (GTER) in children.

Short History of the Gastric Tube

The history of the gastric tube oesophageal replacement began at the turn of the nineteenth century when several surgeons in Europe and North America started experimental work on replacement of the oesophagus. The modern era began with Pr Amza Jiamu, Professor of Surgery at Bucharest, Romania. Between 1910 and 1936, he devised and successfully performed many gastric tube operations on animals [38]. He performed these experiments with his assistant Dr Dan Gavriliu but never performed these operations on humans (Fig. 29.1).

Thus, the use of a well-vascularised graft, such as the gastric tube, as an oesophageal replacement in humans is not a new concept but owes its current popularity to the pioneering work of Dr Dan

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Gavriliu, a general surgeon from Bucharest, Romania. In 1951, Dr Gavriliu reported his first series of 21 reversed gastric tubes in adults [39]. Initially he positioned the tube presternally and latterly retrosternally, although he never used the transpleural or mediastinal routes. In his original description of the procedure, he recommended routine splenectomy in order to facilitate the tailoring of a gastric tube of sufficient length to reach the neck without tension and to improve blood flow within the tube by diverting splenic blood into the stomach. Finally, he wrapped the tube in omentum. There are no data to confirm the value of these complementary procedures. In 1957, he published a book on surgery of the oesophagus which broadened acceptance of the procedure throughout Romania, Europe and ultimately North America [40, 41].

In America, Dr Heimlich from Ohio, without knowing of the work and publications of Dr Gavriliu, described a similar technique and published his experience in 1959 [42]. The first reversed gastric tube oesophageal replacement (RGTER) in Canada was performed by Dr. James Fallis, and Dr. S Ein has extensively used the procedure in children and published long-term results [16, 17, 35, 43].

More recently, Burrington [44] and Pederson [4] have reported short series of gastric tube oesophageal replacement (GTER) in patients with long-gap oesophageal atresia performed in the neonatal or early infancy period.

Fig. 29.1 Dr Dan Gavriliu when being a visiting Professor in the USA

Over time, several modifications of the procedure have been developed including transhiatal oesophagectomy [45–48], which was later incorporated into a one-stage operation with colonic interposition by Rodgers [48].

In recent years, the most common procedure for paediatric oesophageal replacement has been a combination of transhiatal oesophagectomy and replacement of a substitute (colon, small bowel, gastric tube or whole stomach) through the posterior mediastinum in a one-stage operation. For the reversed gastric tube, the first report of such a one-stage procedure was published by Ionescu in 1985 [18].

Surgical Anatomy of the Gastric Tube

In this section, the vascular anatomy relevant to the creation of a gastric tube is discussed. For details on other aspects of gastric anatomy, please see the chapter devoted to anatomy.

Any oesophageal replacement must be well vascularised. Every large series of oesophageal replacement has a few cases of graft failure due to vascular causes (thrombosis, poor perfusion, compression or twisting of the pedicle) [49, 50]. Some surgeons recognizing these difficulties have combined replacements with additional microvascular anastomosis in the neck (with facial, internal mammary or even external carotid arteries) in order to provide additional blood flow [19, 21]. The stomach has a rich vascular network with multiple anastomosis and its acid secretion reduces the risks of infection. As the majority of surgeons use the reversed gastric tube as an oesophageal replacement, the discussion here is focused on the blood supply of the greater curvature of the stomach. The greater curvature of the stomach is bordered by the gastro-epiploic arcade (gastro-omental) representing an anastomosis between the left (taking origin from the splenic artery) and the right (taking origin from the left gastric artery) gastro-epiploic arteries. Multiple collateral vessels course within the wall of the greater curvature where they make large loops in a rich anastomosis.

In some cases, the arcade bordering the greater curvature is incomplete. A vascular gap of anything between 2 and 7 cm might raise concern in the mind of the surgeon about the quality of blood supply available for the perfusion of a gastric tube. This "long gap" was seen in 30 % of the cases in my personal experience of 109 reversed gastric tubes. Studies of the microvascular anatomy of the stomach confirm the excellence of the vascularity, and such short gaps in the arcade are not a contraindication to the use of the gastric tube. Several studies have shown that the fundus of the stomach is not as well perfused as the body or the antrum. It might therefore appear that a tube based on the right gastro-epiploic vessels would have some deficiency of vascularity at the fundal end, in contrast to the standard iso-peristaltic tube based on the left gastro-epiploic vessels [51]. However, in clinical practice, there is no difference in the quality of blood supply in either iso- or antiperistaltic tubes (Fig. 29.2).

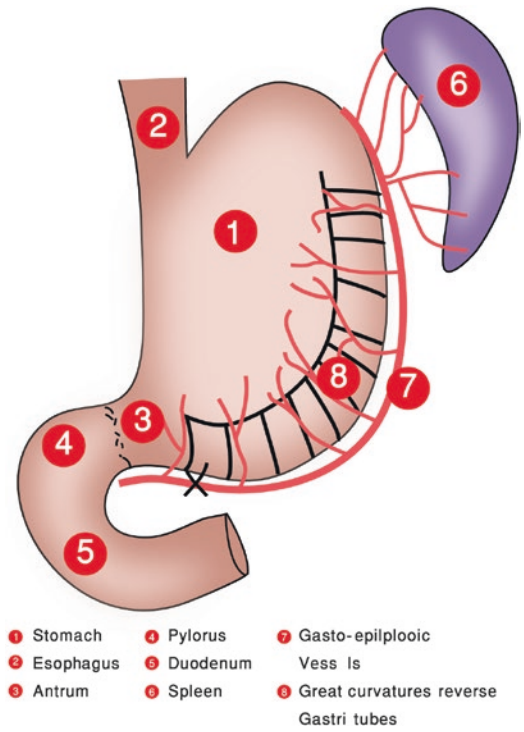

Fig. 29.2 Vascular anatomy of the gastric tube (Illustrated by M. Hassanieh)

Using Doppler flowmetry studies of both iso- and antiperistaltic tubes (with right or left gastro-epiploic blood supply), Shilling [51] concluded that the fundus was a well-perfused area of the stomach and suggested a gastric tube based on lesser curvature vessels (fundus rotation gastroplasty), which is technically challenging and may provide insufficient length. They further recommended the use of an intraoperative Doppler study to allow early detection of a poor vascular graft with risk of ischaemia [52]. In 2006, Nishikawa studied 13 gastric tubes used for oesophageal replacement measuring thermal images during the procedure [53], clearly demonstrating a lower surface temperature at the cranial end of the tube, suggesting reduced perfusion. It was concluded that intraoperative thermography, a non-invasive, reliable test, should be used to guide construction of a gastric tube [53]. Lazar [54] proposed the use of thoracic epidural anaesthesia to improve the microcirculation when a gastric tube is constructed.

In surgical practice, most gastric tubes are made as antiperistaltic tubes with no significant increase in the number of vascular complications compared to iso-peristaltic tubes. The authors have no personal experience with indirect methods of assessing perfusion. Some authors have recommended testing the vascularity of the tube by temporary occlusion of the proximal and distal circulation with vascular clamps as is frequently done when preparing a colonic oesophageal replacement. This procedure was performed early in our experience without yielding any useful information; we do not recommend its use.

Incorrect positioning of a previously placed gastrostomy on the greater curvature, particularly if the procedure has damaged the gastro-epiploic arcade, may constitute a contraindication to the creation of a gastric tube. In our experience, two patients presented with this dilemma. In one patient, a colonic replacement was performed with excellent results and the other had an atypical gastric tube created involving the posterior wall of the stomach. Complete necrosis of the graft occurred necessitating removal of the tube

and usage of a colonic interposition. It must be stressed that a preliminary gastrostomy should be placed on the anterior gastric wall as far away from the greater curve as possible.

In conclusion, the vascularity of the stomach offers a well-perfused organ for oesophageal replacement with few anatomical variants and a low risk of vascular failure within the graft, unlike the small bowel or colonic interpositions.

Indications for Gastric Tube Oesophageal Replacement

Medical Indications for Oesophageal Replacement

Long-gap oesophageal atresia [1, 4, 55–59] and extensive stricture following caustic ingestion [9, 17, 60–65] are the most common indications for oesophageal replacement in children. Foker's technique [66–70] of rapid oesophageal elongation, together with various techniques of delayed primary anastomosis [59] including Kimura's progressive elongation of the upper pouch, which remains popular in some parts of the world like Argentina, has almost eliminated the need for oesophageal replacement in EALG [71]. The complete failure of the anastomosis after primary, delayed primary or secondary surgery may still however necessitate oesophageal replacement as a salvage procedure.

The aggressive treatment of caustic injuries with steroids [72, 73], both systemic and local, early dilatation using balloons or endless loop bougienage [74–76] and the use of resorbable stents for resistant strictures [77, 78] have significantly reduced the number of patients requiring oesophageal replacement.

Occasionally, for patients with severe oesophageal stricture due to epidermolysis bullosa [52], achalasia, long oesophageal duplication [79] or infectious stricture [80], a replacement of the oesophagus may be indicated. Historically, gastric tube replacement has been used in a desperate attempt to control bleeding from oesophageal varices [81].

In children, oesophageal malignancies are rare indications for oesophageal replacement. In our experience, there are only two patients, one with an adenocarcinoma of the oesophagus and one with an aggressive infantile fibromatosis of the neck and mediastinum with involvement of the oesophagus.

Finally, gastric tubes have been used in selected cases for other purposes such as drainage for a ventricular shunt (ventriculo-gastric shunt) in biliary atresia (porto-gastrostomy) and as a palliative short iso-peristaltic tube as a continent, tubeless gastrostomy in patients with unresectable oesophageal cancer.

Choice of Type of Replacement

The choice of technique for oesophageal replacement very much depends upon each surgeon's preference and experience with the two most popular being colonic interposition [5–9, 49, 82] and RGTER [1, 14, 16, 17, 36, 37, 58, 60, 83, 84]. Since the early 1980s, total gastric transposition, popularized by Lewis Spitz, has been extensively used in England and North America [11–13, 23, 24]. A very small stomach as seen in early type 1 oesophageal atresia; gastric scarring from caustic ingestion, especially the ingestion of strong acids; an inappropriately placed gastrostomy that impinges on the greater curvature; or patients with previous gastric surgery, such as Nissen fundoplication with or without gastrostomy, all make gastric tube construction hazardous.

However, GTER is the preferred option when a colonic graft is unavailable as may be seen in VATER/VACTERL syndrome with a previous colostomy, oesophageal atresia associated with malrotation, congenital megacolon, congenital short colon, previous episodes of necrotizing entero-colitis, multiple intestinal atresia, etc.

Despite several small series with good results after jejunal interposition [19, 20], the vascular risk, the frequent need for an additional microvascular anastomosis in the neck, the quality of the graft and the need for two intrathoracic

anastomoses make small bowel interposition a less favoured option.

Harmel [52] performed oesophageal replacements on two siblings with epidermolysis bullosa and severe strictures: one a RGTER and one a colonic interposition. He reported that the gastric tube was performed more easily and more quickly than the colonic interposition but that the results were good in both cases.

Total gastric transposition, although a popular and safe procedure, should be used with caution pending assessment of the long-term quality of life provided and the severity of side effects such as delayed gastric emptying and bile reflux.

Other replacements such as small bowel, gastric tubes fashioned from the fundus or lesser curvature, Scharli's partial gastric transaction [85, 86] should all be reserved for use in the exceptional circumstances when both GTER and colonic interposition are contraindicated.

Planning a Gastric Tube Oesophageal Replacement

Optimal Time for Oesophageal Replacement

The best time for oesophageal replacement depends upon many factors: primary disease, comorbidity, the availability of post-operative intensive care and often an arbitrary policy of the surgeon (e.g. not earlier than 1 year of age or 6–8 kg). In children with oesophageal atresia, there is general agreement that repair or replacement should be performed as early as possible in order to establish oral feeding [1, 4, 44, 55, 57, 58]. All types of replacement (gastric tube, colonic interposition and gastric transposition) have been successfully performed in the neonatal period or early infancy. A large volume stomach is the most important requisite for a successful gastric tube as it enables the gastric reservoir to be preserved, along with normal motility and gastric secretion. In pure oesophageal atresia, the stomach is notoriously small; after several months of gastrostomy feeding, an increase in volume can be anticipated (Fig. 29.3) allowing the safe construction of a gastric tube. Most of the patients in our series underwent gastric tube oesophageal replacement around 1 year of age.

In patients with extensive oesophageal strictures resistant to dilatation, replacement is indicated when it is recognized that all methods have failed to relieve stricturing. In our experience, dilatation using an olive dilator passed over a string which is passed from nose to gastrostomy in an endless loop is effective at reducing the need for oesophageal replacement [74, 75, 79]. This method has the advantages that it can be done twice daily, without anaesthesia, at home by the mother, or the patient himself. It is a safe procedure with few complications (nasal, choanal, soft palate ulcerations, granuloma, etc.) and allows concomitant oral feeding. These advantages must be weighed against the need for a gastrostomy and the permanent presence of a string passing from the nose and the potential psychological stress of such a procedure (Fig. 29.4).

Replacement should not be attempted within 6 months after the initial injury. Some authors suggest earlier replacement based on the intuitive belief that progressive mediastinal fibrosis will develop over time making transhiatal oesophagectomy hazardous [9]. Following previous mediastinitis, iatrogenic perforation during dilatation, pleural effusion or empyema, a minimum interval of 1 year is advised, particularly if a posterior mediastinal replacement is planned. In some patients, it may be prudent to place the graft retrosternally. The damaged oesophagus should always be removed, preferably at the time of reconstruction, but alternatively as a second procedure [87].

Pre-operative Preparation for Gastric Tube Oesophageal Replacement

Oesophageal replacement is a major operation irrespective of the technique chosen. Post-operative morbidity and occasional mortality are recorded in most series. In some countries, a nationally accepted protocol for oesophageal replacement is in place and patients are referred to selected tertiary centres of excellence, and

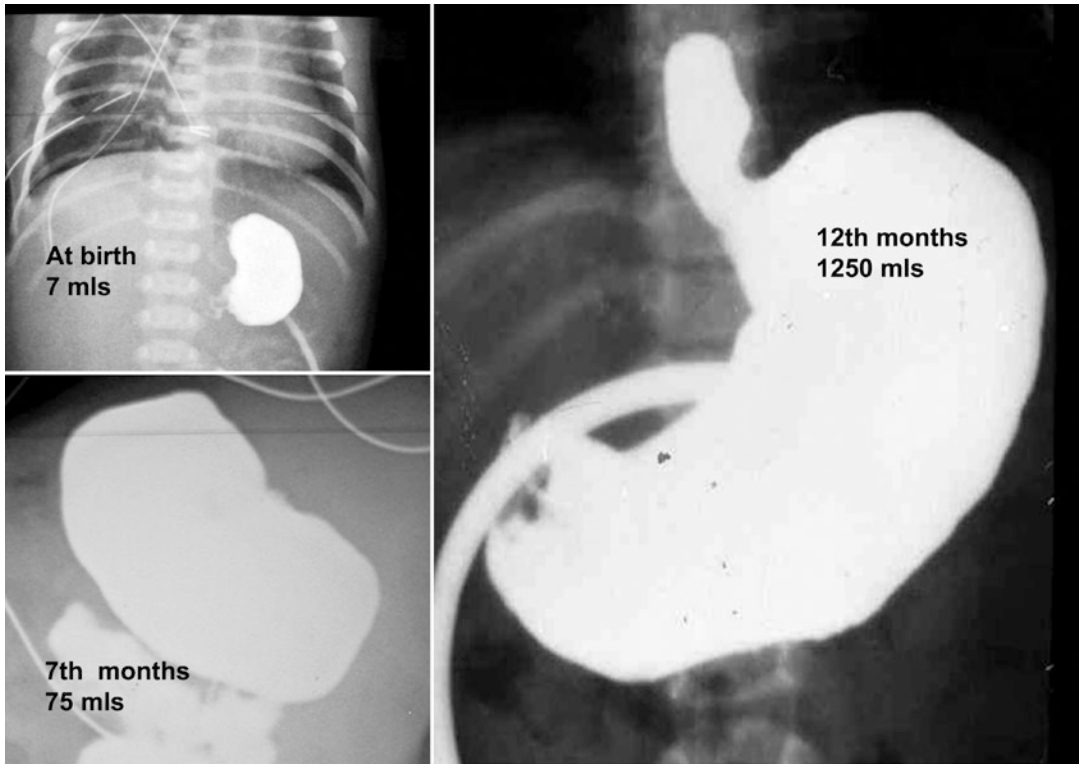

Fig. 29.3 Under feeding through the gastrostomy, the progressive increase in volume of the stomach is noticed (EALG)

these operations are performed by experienced surgeons and patients cared for by specialized ICU staff.

Pre-surgical care should be provided ideally by a multidisciplinary team including a paediatric gastroenterologist, nutritionist, pulmonologist, experienced endoscopist, stoma care staff, experienced surgeon and anaesthetist and should also include a psychologist for family and older child support. Prior to surgery, several conditions must be discussed.

Tracheostomy

The decision to perform a RGTER should be reviewed to ensure that it is the right operation for the right patient. The optimal timing of surgery has been discussed. Many children, however, particularly those with malformation syndromes or caustic injuries present with severe malnutrition. Improving the nutritional status of the patient is an essential part of pre-operative preparation; this can take months.

Some patients will have had a tracheostomy performed for various reasons. The presence of a tracheostomy is not an absolute contraindication to oesophageal replacement, but it does increase the risk of complications at the cervical anastomosis. So, if possible, surgery should be delayed until removal of the tracheostomy has been accomplished. Four patients in our series had tracheostomies in place at the time of surgery and replacement went without incidents.

Enterostomies

Most patients presenting for oesophageal replacement will have a feeding gastrostomy in place, usually of the Stamm variety. Sometimes the gastrostomy has been performed elsewhere and could be inappropriately sited or giving rise to complications such as leakage, inflammation or skin erosion caused by gastric acid. In a few cases, it may be wise to close an existing gastrostomy and reopen a new one as a preliminary step before oesophageal replacement. The surgeon

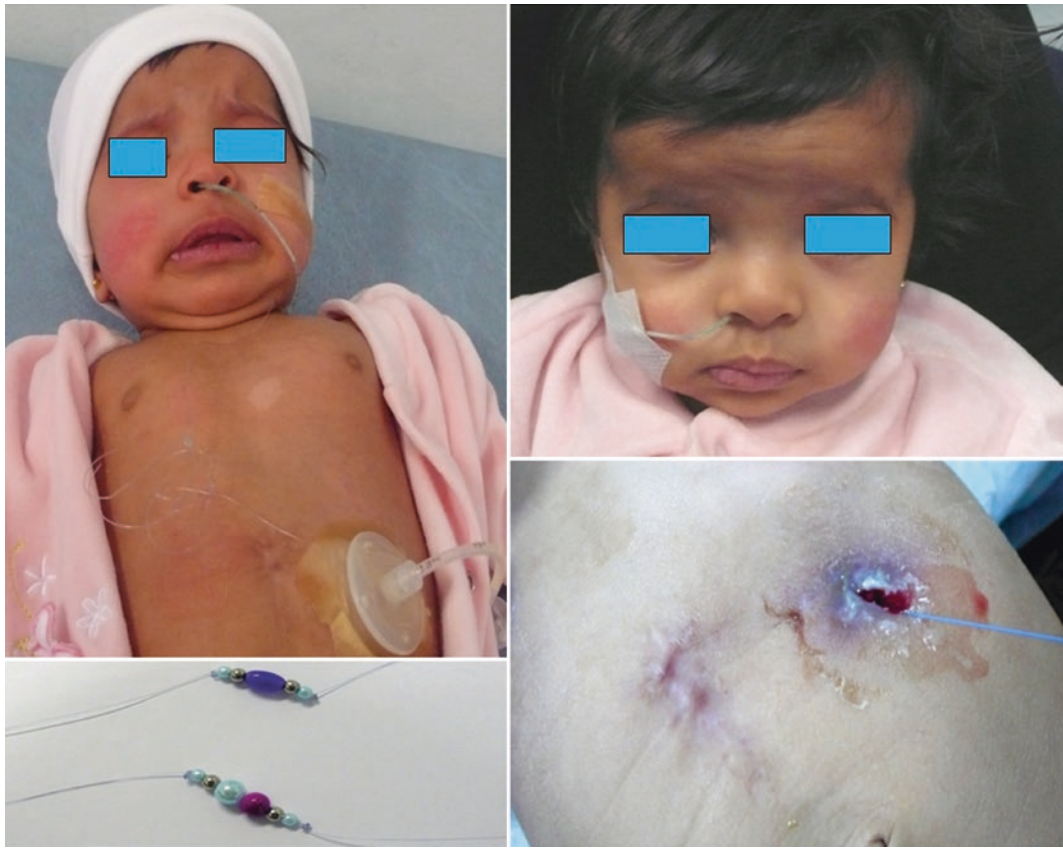

Fig. 29.4 Endless loop dilatation for severe stricture of the anastomosis and hypoplastic lower oesophageal segment after Foker's technique

who performs such a revision must make careful note of the gastric blood supply.

Some surgeons have advocated a feeding jejunostomy in order to leave a stomach undisturbed by previous surgery; however, a gastrostomy has the effect, not only of allowing intermittent feeding but also of enlarging the gastric reservoir. After several months of feeding via a jejunostomy, the stomach becomes very small and a gastric tube may no longer be possible. If a patient presents with a jejunostomy in place, this should be closed and a gastrostomy created, particularly if the stomach is small. An alternative would be to plan a colon interposition rather than attempt to create a gastric tube from an inadequately sized stomach. Feeding via a gastrostomy should be given as a bolus which should reach 250–750 mls depending upon the age of the patient.

In patients with cervical oesophagostomy and long-gap oesophageal atresia, a programme of sham feeds is essential and should be implemented immediately after birth. In patients being treated by continuous pharyngeal suction, sham feeds can be simulated by having the baby suck on an empty bottle.

Contrast Studies

Pre-operative contrast studies of the stomach and colon have been recommended. In our experience, these pre-operative studies are not necessary.

Bowel Preparation

The day before surgery, a full bowel preparation using Golytely® or Kleenprep® should be carefully performed. Should intraoperative findings mandate a change from gastric tube to colonic interposition, it is essential to have a fully

prepared bowel. The operating surgeon must be prepared to perform any type of oesophageal replacement. In our series, two patients were switched intraoperatively from a gastric tube to colonic interposition and one from a planned colonic interposition to a gastric tube.

Informed Consent

A comprehensive informed consent is crucial and should be taken by the surgeon who will perform the operation. Obviously, the planned operation will be described as well as the possible complications. Alternative techniques must also be explained. The use of a short video of the operation is recommended.

The Standard Technique of Reversed Gastric Tube Oesophageal Replacement

General Data

We describe here the technique for the most popular oesophageal replacement procedure, the reversed or antiperistaltic gastric tube. This description is based on our series of 109 operations performed by the same team of surgeons between 1975 and 2009 [18, 37, 88].

Broad-spectrum antibiotic prophylaxis is given 30 min before surgery and maintained for 3–5 days. Good venous access is assured by insertion of double-lumen central line.

The left side of the neck from the angle of the jaw and the whole chest and abdomen are meticulously prepared and draped using Opsite® (Fig. 29.5). In adults, the operation can be performed by two surgical teams working simultaneously: one intra-abdominal, preparing the gastric tube, and the other preparing the neck. In children, the operation is performed by a single surgical team.

Tailoring the Gastric Tube

Through a midline laparotomy incision, the stomach is approached and inspected. The gastrostomy tube is pulled out and the site of the gastrostomy is separated from the abdominal wall and the stoma is temporarily closed. Great care should be taken to avoid damage to the vessels along the greater curvature; the left triangular ligament of the liver is divided and the lower oesophagus is prepared as if for a fundoplication. The vagus nerves are identified and separated from the oesophagus. Often the posterior vagus is not clearly visible, but its identification is not essential. No upward dissection of the oesophagus or oesophageal stump is performed at this stage in order to prevent an accidental pneumothorax or, worse, bleeding from the mediastinum at the beginning of a long operation.

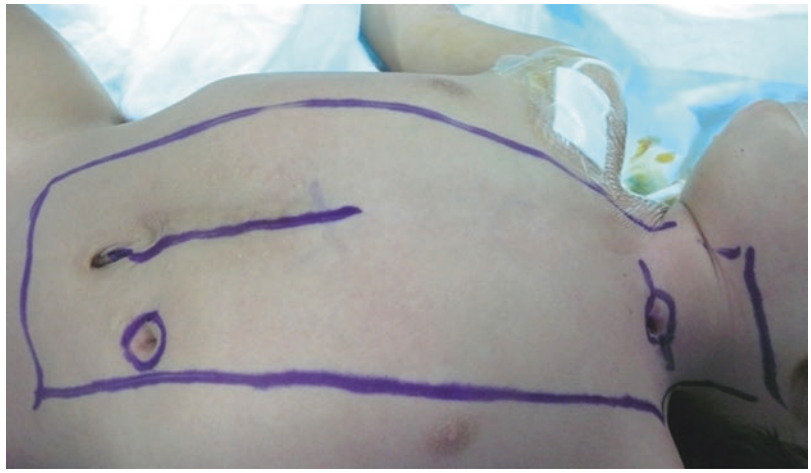

Fig. 29.5 Preparation of the operative field for RGTER in case of EALG

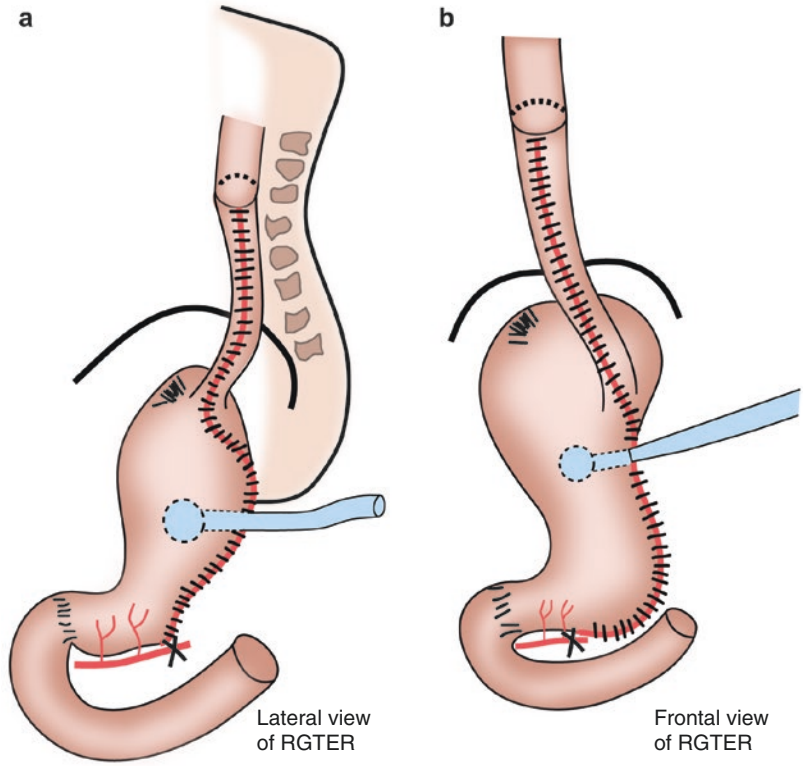

Fig. 29.6 (**a**, **b**) Configuration of the reversed gastric tube (Illustrated by M. Hassanieh)

On the greater curvature, the site from which the gastric tube will be divided is marked with a transfixion suture. The length of tube that is required is measured with a feeding tube from the middle third of the greater curvature to the mastoid process.

Usually the tube starts 2–5 cm to the left of the pylorus on the antrum. The gastro-epiploic vessels are identified but not yet divided. It is still possible to perform either an iso-peristaltic tube or an anti-peristaltic tube. The gastro colic omentum is progressively divided from right to left. The greater omentum remains attached to the colon and the gastro-epiploic arcade stays with the stomach. In his original description, Gavriliu recommended mobilization of the spleen and even splenectomy. These manoeuvres are no longer recommended.

The calibre of the gastric tube is very important and should be approximately the diameter of the native oesophagus. For modelling the tube, we suggest a chest drain tube size CH 10–14 for babies and size 18–22 for older children. The gastric tube is then separated from the greater curvature (Figs. 29.6 and 29.7). A decision must now be made whether to create an iso- or an anti-peristaltic tube and the appropriate gastro-epiploic artery is divided.

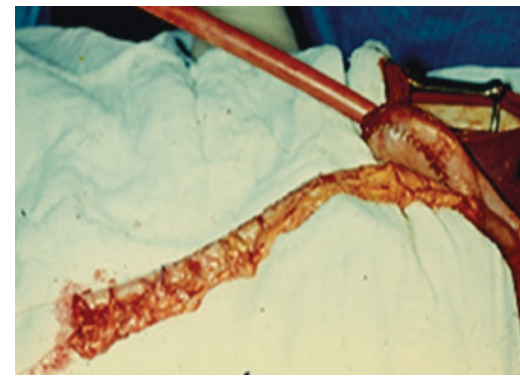

Fig. 29.7 An old-fashioned hand-sutured gastric tube

The gastric tube itself can either be created with hand suturing or using mechanical staples. A 2 cm incision is made on the antrum at the chosen

level and the chest tube inserted towards the oesophagus and held against the greater curvature. To prevent unnecessary blood loss, pairs of transfixion sutures are placed over the vessels during separation of the gastric tube, using a Vicryl® suture on a straight needle. These sutures will be removed as the gastric tube is developed (P. Orsoni [2]). The gastric tube is separated from the body of the stomach and progressively tubularized. The first 3–5 cm of the gastric tube should be wider than the rest of the tube giving a funnel shape which is preferable for cervical anastomosis. In our series, the first 97 gastric tubes were all hand-sutured. The first 3–5 cm of the tube is created with interrupted absorbable sutures in two layers (Vicryl®, PDS®, Monocryl®). The rest of the tube can be quickly made using a continuous suturing of similar material in two layers. The gastrostomy tube is re-positioned, usually through its original site. Often the gastrostomy can comfortably be accommodated in the long suture line that reconstitutes the greater curvature. In babies, we prefer the handmade gastric tube which only takes 10–15 min to complete. The gastric tube must be made watertight, and this is checked by filling it with saline under moderate pressure.

The most recent 13 gastric tubes (since 1993) have all been created using stapling devices (Ethicon® linear stapler either 55 or 75 mm). This is a fast and easy technique and even a very long gastric tube can be created in 10–15 min.

At the chosen level on the antrum, a 2 cm incision on both the anterior and posterior wall is made, the chest tube which acts as a template is inserted and the linear stapler is deployed as close to the chest tube as possible. The division is bloodless. In older children, the staple height should be 11–14 mm. Any leak due to faulty stapling could create life-threatening complications (one personal case complicated by mediastinitis). It is now usual to oversew the mechanical suture line with a continuous absorbable suture (e.g. PDS® 3/0–5/0) along both the tube itself and the reconstituted greater curve. In the most recent three cases, the use of endosurgery linear cutting devices, with three layers of staples, made the suture line very secure (Endopath®, ETS Flex 60® or Endo GIA Universal; 12 mm®) (Fig. 29.8).

The gastric tube should nonetheless still be checked with saline under moderate pressure to identify any leak. To supplement either the suturing or stapling of the tube, the wounds can be sealed with biological glue (Tisseal®) to further decrease the risk of leakage. Although not confirmed in a prospective study, we have regularly used Tisseal® to seal the gastric tube, and this technique has recently been reported as a supplement to sutures at cervical anastomosis [89].

Conventional (Iso-peristaltic) vs. Reversed (Antiperistaltic) Gastric Tube?

It has been confirmed by video-recorded contrast studies and 24 h manometry studies that there is no regular peristaltic activity in a gastric tube; the passage of food through the tube depends upon gravity. There is therefore no peristaltic reason to prefer one conduit over the other, although there are still some surgeons performing iso-peristaltic tubes in the belief that this improves propulsion. However, experience in both adults [90] and children [91] confirms the higher morbidity and mortality associated with iso-peristaltic tubes (Figs. 29.9 and 29.10), with some patients requiring a secondary gastrostomy or jejunostomy for feeding.

At the beginning of our experience with gastric tube oesophageal replacement, two patients had iso-peristaltic tubes fashioned. Both patients developed anastomotic fistulae which closed spontaneously in one child, but which required revision in the second. One of these children presented with severe dumping syndrome that persisted for many years, due to the rapid passage of food through the antrum and pylorus, bypassing the gastric reservoir. In both patients, contrast studies failed to show regular peristaltic waves, only some non-propulsive contractions.

We think that iso-peristaltic tubes should only be considered when anatomical conditions preclude the use of an antiperistaltic tube.

Compared to the reversed gastric tube:

- The iso-peristaltic tube is less well perfused at the craniad anastomotic site.
- The iso-peristaltic tube has to be made much longer.

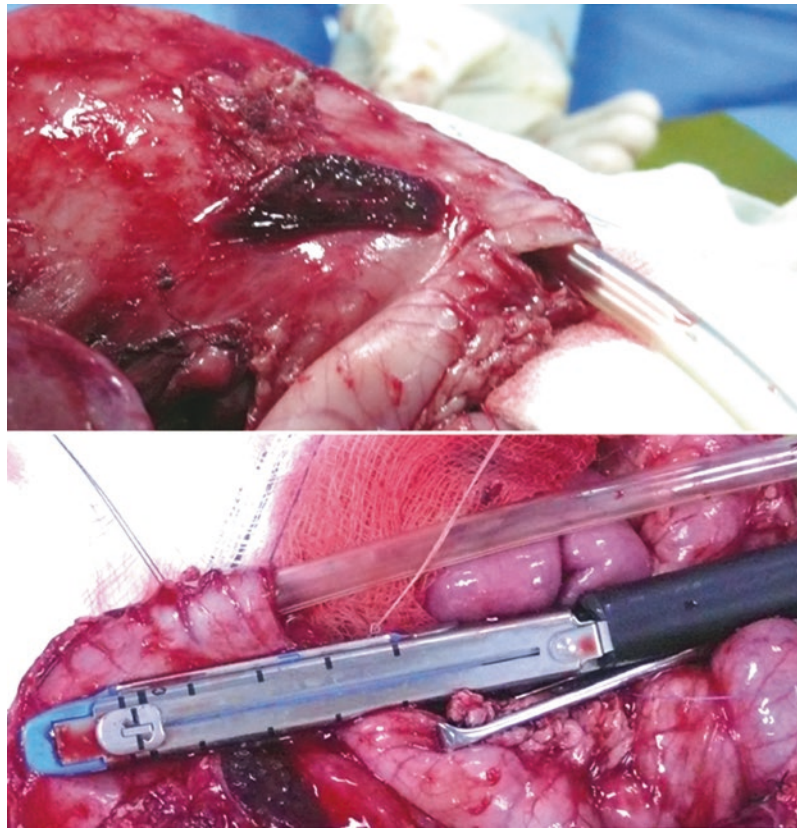

Fig. 29.8 A reversed gastric tube is separated from the great curvature with Endo GIA cutter

- When creating an iso-peristaltic tube, the stomach and duodenum must be expensively mobilized to allow the conduit to reach the neck.
- There is no evidence of propulsive peristaltic activity in any gastric tube.
- The iso-peristaltic tube could complicate dumping syndrome.

Pyloroplasty: Is It Really Necessary?

Pyloroplasty is a standard adjunct to total gastric transposition and added by many surgeons when the oesophageal substitute is brought through the posterior mediastinum. Pyloroplasty or pyloromyotomy is intended to prevent delay in gastric emptying due to the inevitable damage to the vagus nerves. The use of pyloroplasty has not been studied in a prospective fashion. In our series, no patients had a pyloroplasty nor a pyloromyotomy and no problems with gastric emptying have been observed. In our view, these procedures are unnecessary and occasionally lead to complications. Dumping syndrome as well as bile reflux into the stomach and oesophageal substitute have been recorded, and their treatment is often unsuccessful.

Route of the Gastric Tube to the Neck

There are only four possible routes for an oesophageal substitute to traverse the thorax: presternal, retrosternal, transpleural (placed within the cost vertebral angle) or posterior mediastinal, using the normal anatomical position of the oesophagus. Currently the transhiatal posterior mediastinal route is the preferred route in both adults and children (90 cases 83 % in our series), and other routes are reserved for difficult cases with abnormal anatomy [45–48].

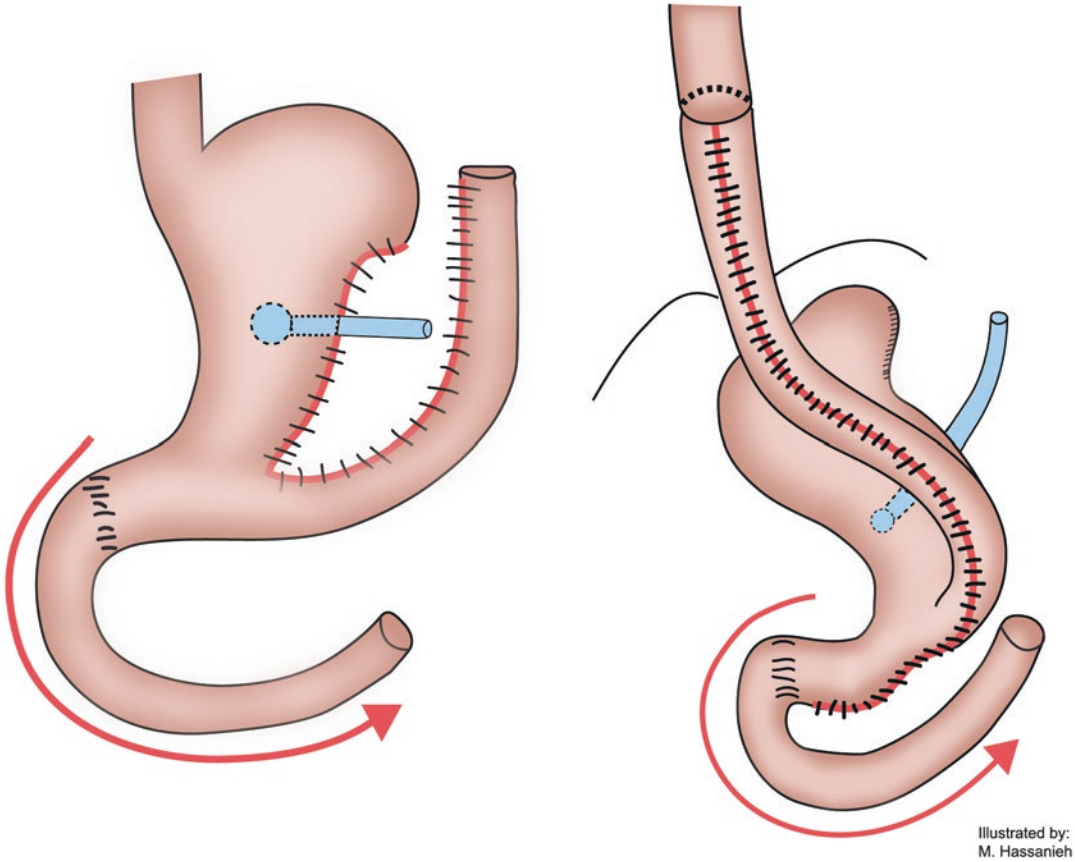

Fig. 29.9 The iso-peristaltic gastric tube (Illustrated by M. Hassanieh)

The digital dissection of the posterior mediastinal tunnel starts at the oesophageal hiatus and proceeds craniad. The dissection should stay strictly in the midline on the vertebral bodies. The cervical oesophagostomy is taken down and a retro-tracheal dissection is started within the posterior mediastinum. If the replacement is being performed for stricture, the dissection proceeds on the wall of the oesophagus.

The transhiatal and cervical dissector fingers meet in the posterior mediastinum and create a wide and comfortable space (Fig. 29.11). A lateral widening of the tunnel is recommended with care being taken not to injure the pleura and create a pneumothorax. The gastro-oesophageal junction is transected and closed with a linear stapler.

A large catheter is now passed from the neck to the oesophageal hiatus, and the gastric tube is attached to the catheter and gently pulled up under direct vision. The long suture line on the tube should be placed anteriorly to avoid twisting. About 2–0.5 cm of gastric tube should remain within the abdomen in order to minimize gastro-gastric tube reflux. Together with the gastric tube, a strong silk thread is passed through the posterior mediastinum, and this will be used to accurately position a long 6–16 mm J-vac® suction drain. This emerges through a short incision in the neck.

Indications for choosing the retrosternal route and the required technique are presented elsewhere.

Cervical Anastomosis

Before any anastomosis is attempted, the perfusion of the gastric tube should again be checked. In most cases, the robust nature of the blood supply is obvious with a pink gastric tube and bleeding

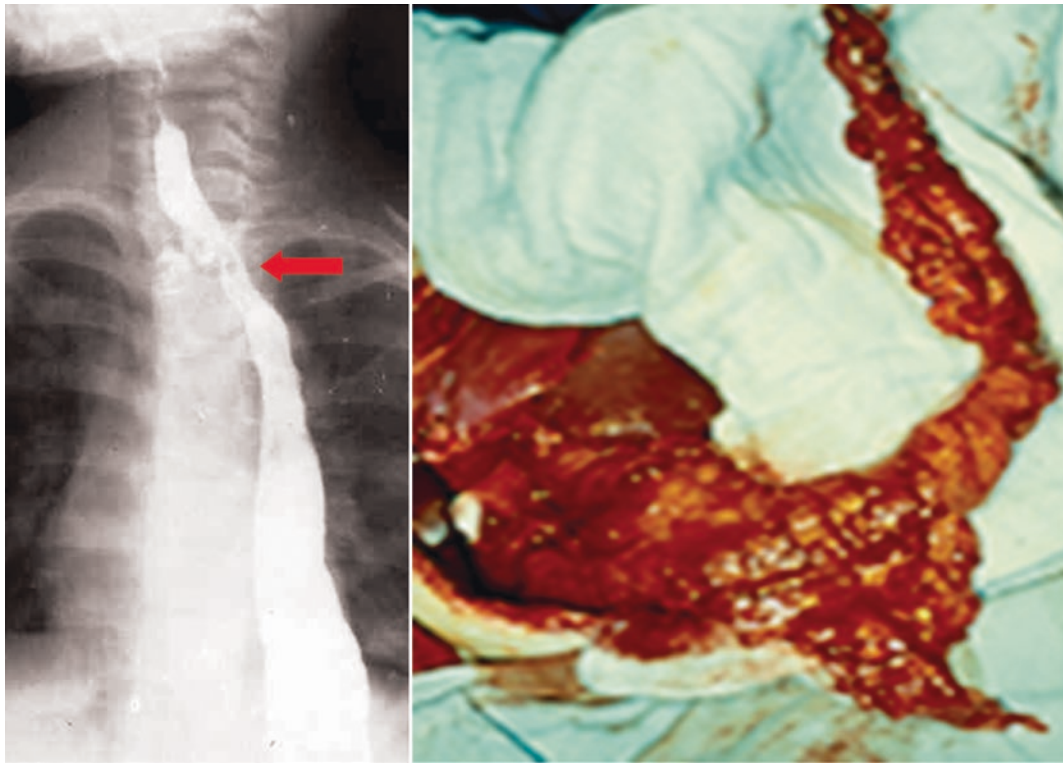

Fig. 29.10 Intraoperative view of an iso-peristaltic gastric tube

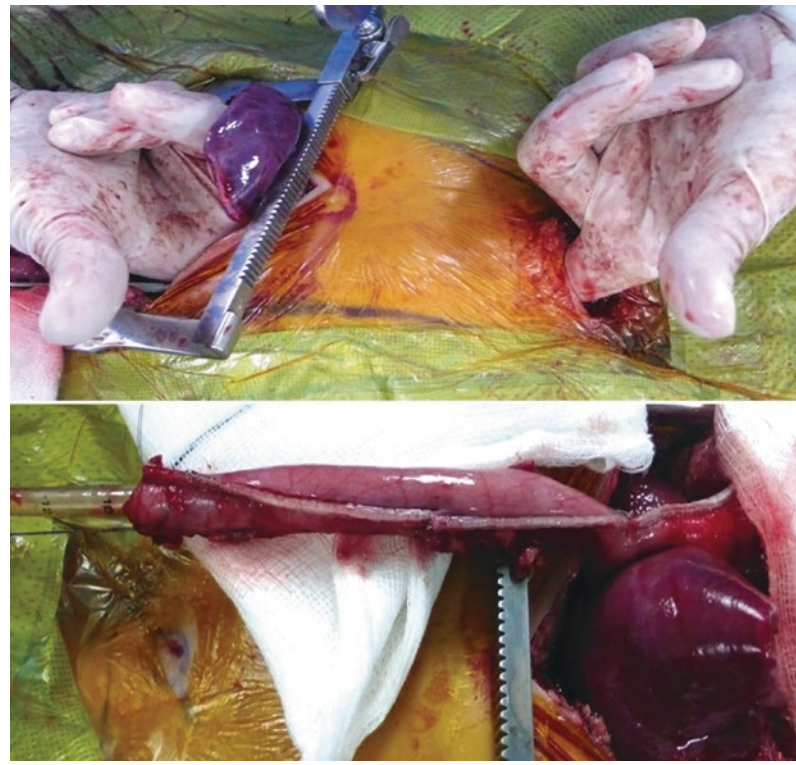

Fig. 29.11 Blunt transhiatal digital dissection of the posterior mediastinal route (*Top*). The gastric tube made with a stapling technique (*bottom*)

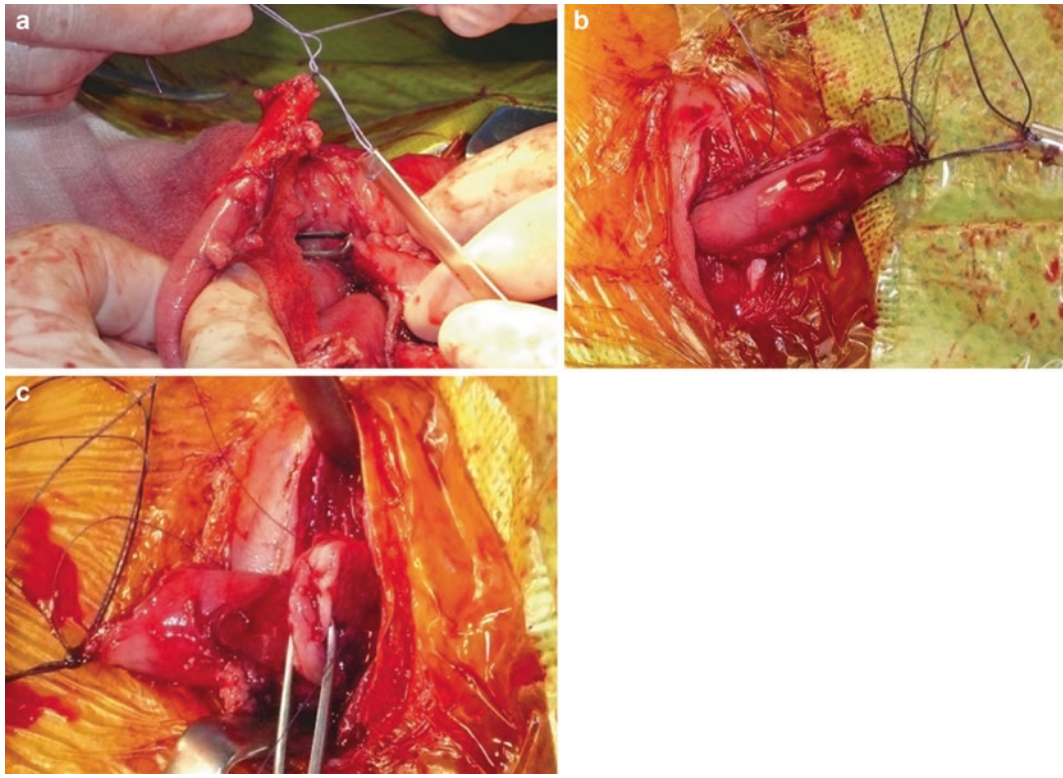

Fig. 29.12 Pull-up of the gastric tube to the neck via posterior mediastinal route and end-to-end gastric tube – oesophagus anastomosis

mucosa (Fig. 29.12). It is prudent to trim 1–2 cm of the tube to allow healthy non-traumatized tissue to be used for the anastomosis.

It is therefore important that the proximal end of the tube is closed with interrupted sutures as the use of a continuous suture would not allow this trimming. If the gastric tube is blue or has obvious ischaemia, the entire tube must be checked for a cause (kinking, compression, torsion, damage to the supplying vessels, etc.). If concern about the perfusion persists, the tube must be pulled back into the abdomen and carefully inspected. Often this restores perfusion and allows widening of the mediastinal tunnel. Rarely damage to the gastro-epiploic vessels leads to a definitely ischemic tube. Such a tube must be removed and another replacement option chosen, either at the same operation or at a later date. It is important to make the tube initially "too long" as an apparently ischemic tube becomes well perfused if trimmed by 1–4 cm.

The anastomosis is made end to end with interrupted 5/0 absorbable sutures, our preference being for PDS®. For the last 47 cases, the cervical anastomosis has been sealed with fibrin sealant (Tisseal® fibrin glue) with a rewarding decrease in cervical fistulae [89]. Recently, this same manoeuvre has been shown also to be advantageous in colo-oesophageal anastomosis [89].

Most cervical oesophagostomies are sited on the left at the anterior border of sternocleidomastoid muscle in its lower third. If the oesophagostomy has been made on the right, the gastric tube simply needs to be a little longer.

At the end of the operation, the gastrostomy is recreated either at the original or at a new site. In our first 10–20 cases, the peritoneal cavity was drained with a Penrose drain, but this is now considered totally unnecessary.

The procedure lasts from 1.5 to 3.5 h (mean 2 h 10 min). The use of mechanical stapling devices makes the procedure much shorter.

Gastric Tube Oesophageal Replacement for Long-Gap Oesophageal Atresia

The standard reversed gastric tube as described above is also used in patients with long-gap oesophageal atresia [1, 57, 58]. In recent years, oesophageal replacement has become an uncommon procedure for EALG and is most commonly needed as a secondary procedure after failure of a primary strategy such as delayed primary anastomosis [59], active elongation using Foker's technique [66–70] or Kimura's elongation of the upper pouch [71]. In our experience, 23 reversed gastric tubes were performed for EALG, but only two were done in the last 10 years: one with oesophagostomy and gastrostomy performed elsewhere and the second after failure of Foker's technique.

The operation is well tolerated in infancy and can be performed as soon as a reasonable gastric reservoir is demonstrated. When oesophageal replacement is indicated in VATER or VACTERL syndromes, a gastric tube is preferred over colonic replacement, particularly in the presence of an anorectal malformation. In complex malformations (e.g. CHARGE syndrome), many children have respiratory diseases requiring a tracheostomy, which increases the risk of a gastric tube oesophageal replacement. Consequently a long delay, often years, is recommended. In many centres, a total gastric pull-up is suggested for such patients, but our experience confirms that a reversed gastric tube oesophageal replacement is satisfactory even in these complicated situations.

The Short Gastric Tube in Long-Gap Oesophageal Atresia

In our limited experience of Foker's oesophageal lengthening procedure, there has been consistent success in the upper pouch, but it has been less effective in the lower oesophagus. In this situation, a short gastric tube with an intrathoracic anastomosis is an attractive option. This may also be an appropriate procedure after Kimura's technique has reached its maximum lengthening (Fig. 29.13).

Gastric Tube Oesophageal Replacement for Severe Oesophageal Stricture and Allied Diseases

In patients requiring oesophageal replacement for caustic injuries or acquired diseases, removal of the diseased oesophagus is mandatory. Several reports of malignancy within a retained oesophagus have been published [87]. In Gavriliu's series, three patients died due to carcinoma in the retained oesophagus. Peptic ulceration, bleeding and cystic transformation of the diseased oesophagus (oesophageal mucocele) have also been reported [92]. Oesophagectomy can be performed after successful oesophageal replacement as a separate operation through a right or left thoracotomy, or transhiatally by blunt dissection or stripping, as part of the replacement operation. This one-stage procedure has become the "gold standard" for most surgeons.

Pre-operative preparations are the same as for any gastric tube oesophageal replacement with a full bowel preparation being performed through the gastrostomy.

The operation begins with a left cervical approach to the oesophagus, identifying and protecting the left recurrent laryngeal nerve and the vagal trunk. The oesophagus is separated from the trachea. A large bore tube is passed into the oesophagus to define the level of the stricture, thus avoiding the risk of performing an anastomosis below a stricture. Three patients in our experience with total gastric transpositions performed elsewhere had the anastomosis performed below an unrecognized moderate stenosis. A soft catheter is passed around the oesophagus in the neck to facilitate manipulation during dissection.

The gastric tube is now fashioned as previously described. Transhiatal oesophagectomy is performed by combined digital dissection upwards from the abdomen and downwards from the neck. Keeping the finger very close to the oesophagus, gentle but firm digital dissection

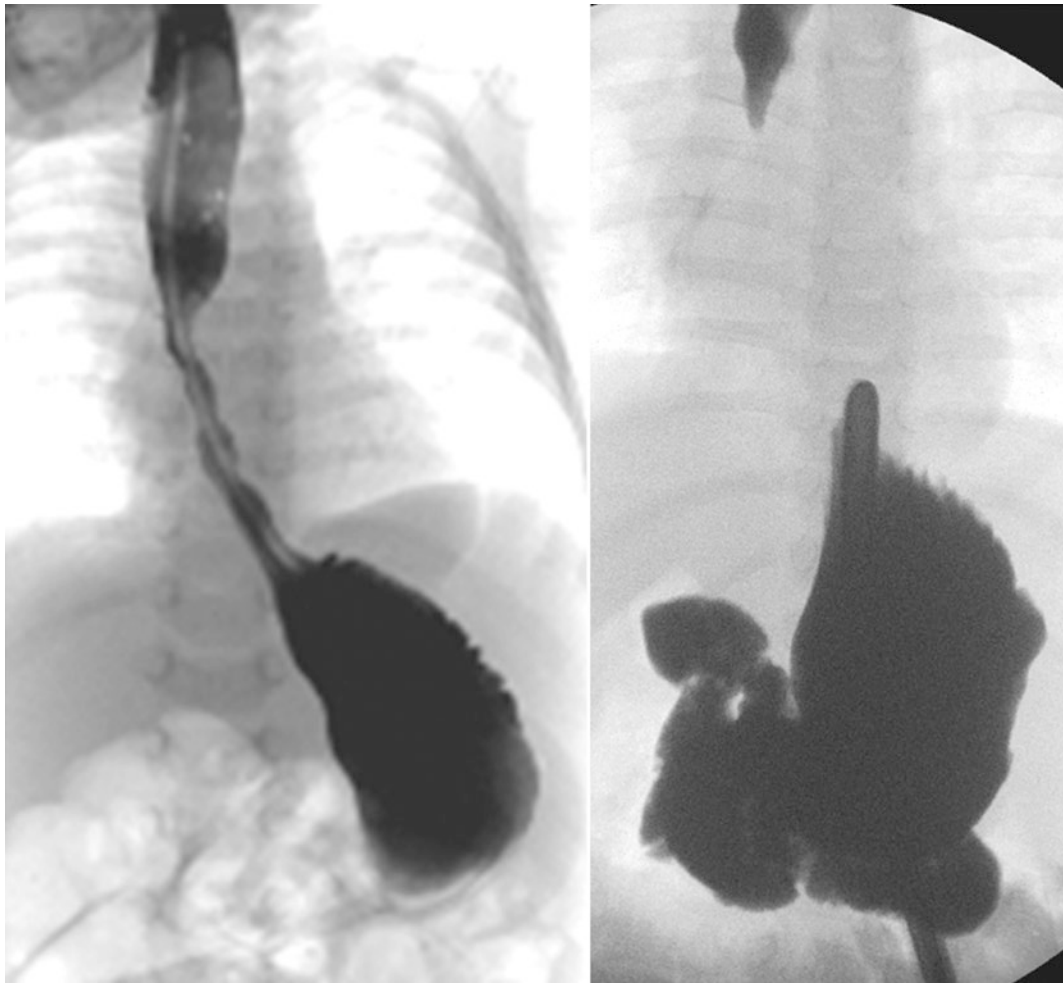

Fig. 29.13 Contrast study in a case of EALG and failure of elongation of the lower oesophageal stump. A short gastric tube with intrathoracic anastomosis is a good option

proceeds uneventfully in most cases with surprisingly little bleeding. The most common complication is a pneumothorax, which may require drainage. Injuries to the aorta, trachea, main bronchus, thoracic duct or pericardium have all been reported, probably reflecting adhesion to the primary pathology. In patients with a documented history of severe mediastinitis due to perforation (pleural effusion, empyema, mediastinal drainage for pus collections, etc.), blunt transhiatal oesophagectomy should be avoided (Fig. 29.14). Pre-operative imaging, no matter how sophisticate, cannot exclude the possibility of catastrophic complications. Two options should be considered:

1. One-stage operation with oesophagectomy performed by open thoracotomy following oesophageal replacement via the mediastinal route.
2. Retrosternal positioning of the gastric tube followed several months later by oesophagectomy. This second strategy is preferred by the authors, but several observations were made:

   (a) The gastric tube should be made longer.
   (b) In the retrosternal position, any tube makes two 90° angulations (at the manubrium sterni and at the site of passage through the diaphragm. Due to these angulations continuous suction of saliva

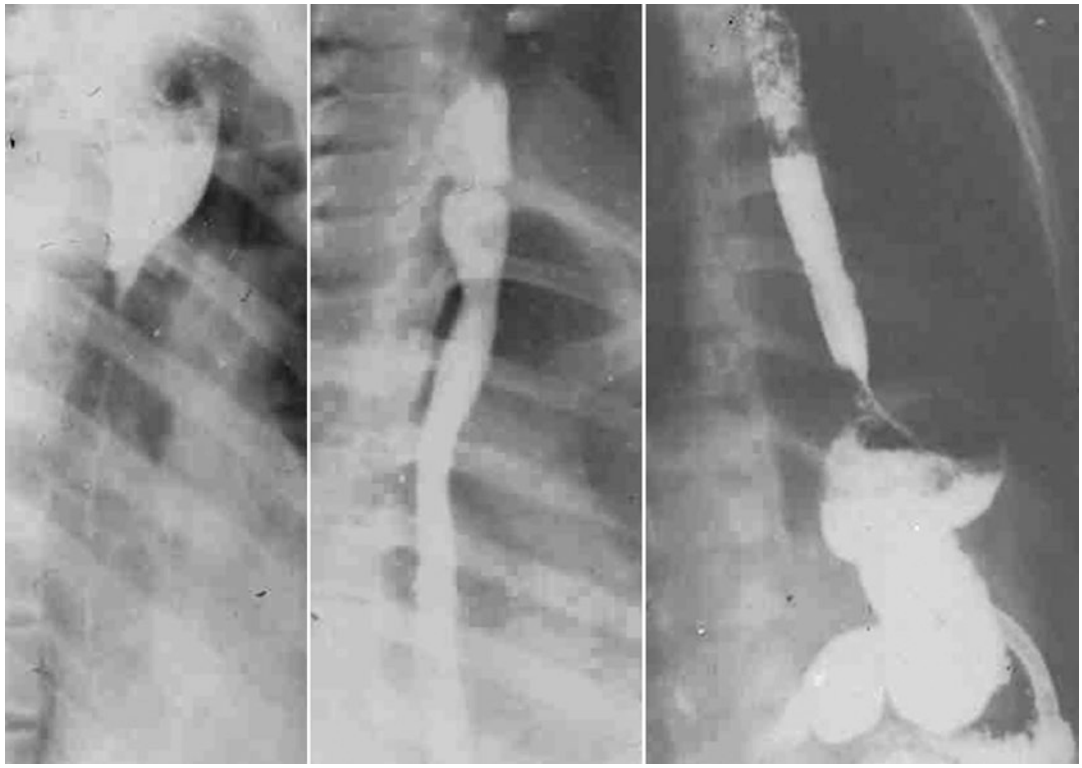

Fig. 29.14 Excellent medium-term result after RGTER for severe stricture sited within posterior mediastinal route

is required in the early post-operative period.

(c) The rate of anastomotic fistula is significantly higher.

(d) In the long term, the gastric tube is prone to progressive dilatation.

(e) Transmission of a bolus through the conduit is slower than when the conduit is in the posterior mediastinum. Often stasis of food within the conduit is noticed.

(f) Follow-up endoscopy of the tube can be difficult or even impossible.

For these reasons, the retrosternal route (Fig. 29.15) should only be used when the mediastinal option is unavailable.

In the case of major bleeding during transhiatal oesophagectomy, the surgeon should not hesitate to open the chest to gain control.

After mobilization, the oesophagus should be freely moveable up and down within the posterior mediastinum. In several teenagers, the digital dissection was not possible, and in these, as in adults, stripping the oesophagus becomes necessary. In three patients, we have removed easily the oesophagus using an ordinary vein stripper without complication.

The completed gastric tube is brought up to the neck through the bed of the oesophagus and end-to-end anastomosis performed.

The Ultra-Long Gastric Tube Including the Duodenum to Allow Concomitant Pharyngeal Reconstruction

In patients with caustic injury resulting in extensive oesophageal strictures, the pharynx may also be involved or completely destroyed [93]. On video fluoroscopy, contrast material is seen to immediately regurgitate through the nose when swallowing is attempted. All of these patients (three in our series) had concomitant laryngeal

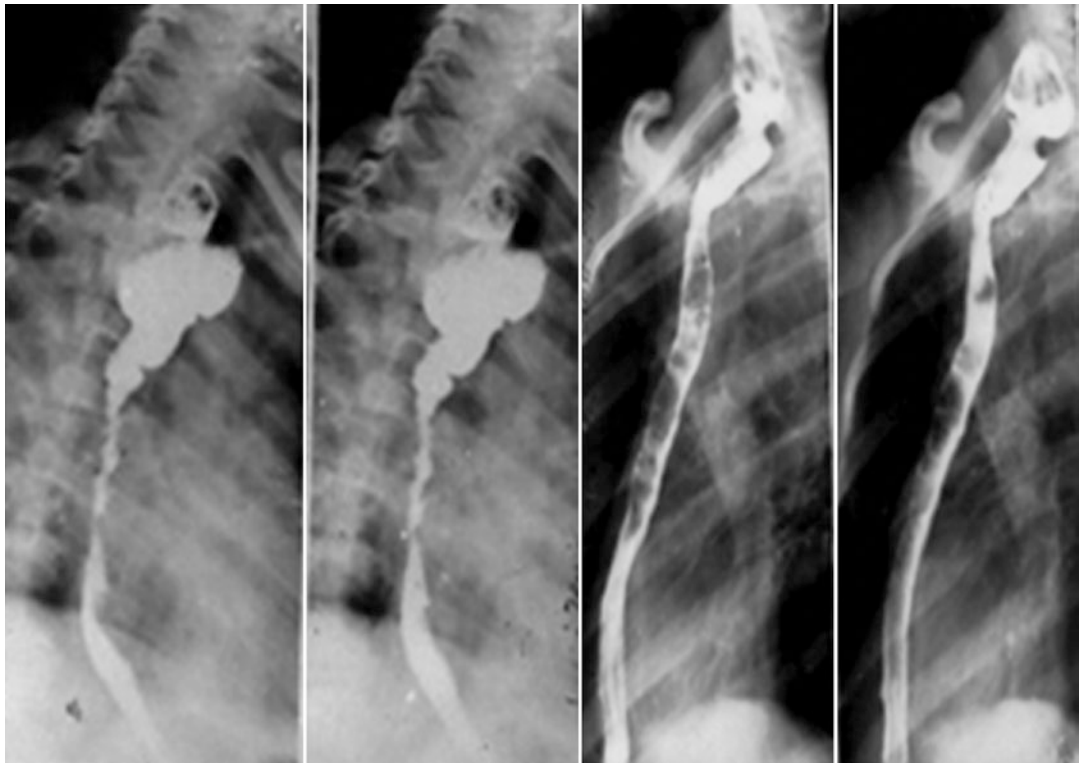

Fig. 29.15 RGTER performed for caustic stricture complicated with mediastinitis. GT positioned retrosternally. Very good result

injury requiring a permanent tracheostomy. The most common approach to this apparent impasse is pharyngeal reconstruction using skin flaps, colon or short bowel segment augmented by a microvascular anastomosis, followed by an oesophageal replacement. The final result is usually disappointing with many repeated operations. Only a few such patients achieve reasonable oral feeding.

Reconstruction of the pharynx and oesophagus can be achieved in a single operation, a one-stage pharyngo-oesophageal reconstruction using the stomach and first part of the duodenum, with transhiatal oesophagectomy [40, 41].

Several modifications of the basic gastric tube operation are required. The operation starts in the neck with a long vertical incision identifying the pharyngeal remnant. An intra-oral finger pushing down in the pharynx facilitates identification and preparation of the later site for the anastomosis. If possible, the anastomosis will be sited on the posterior or lateral pharyngeal wall, and it should be made as wide as possible (Fig. 29.16).

The first part of the duodenum is prepared as for a gastric resection, and it is divided as far distally as possible, meticulously preserving the vascular supply. A Ch18–22 chest tube is placed within the duodenum and passed back into the stomach along the greater curvature. On the antrum, 2–3 cm from the pylorus, a 75 mm linear stapler is placed and the first gastric tube division is performed. Often a very long tube is required to reach the pharynx and the tube usually incorporates the fundus. The longest tube created in our series measured 54 cm (21.5 in.). Gastrointestinal continuity is restored by duodeno-gastric anastomosis. After transhiatal oesophagectomy, the long tube is brought to the neck via the posterior mediastinal route. Pharyngo-duodenal anastomosis is difficult. A multidisciplinary team involving experienced ENT or facio-maxillary surgeons is of great

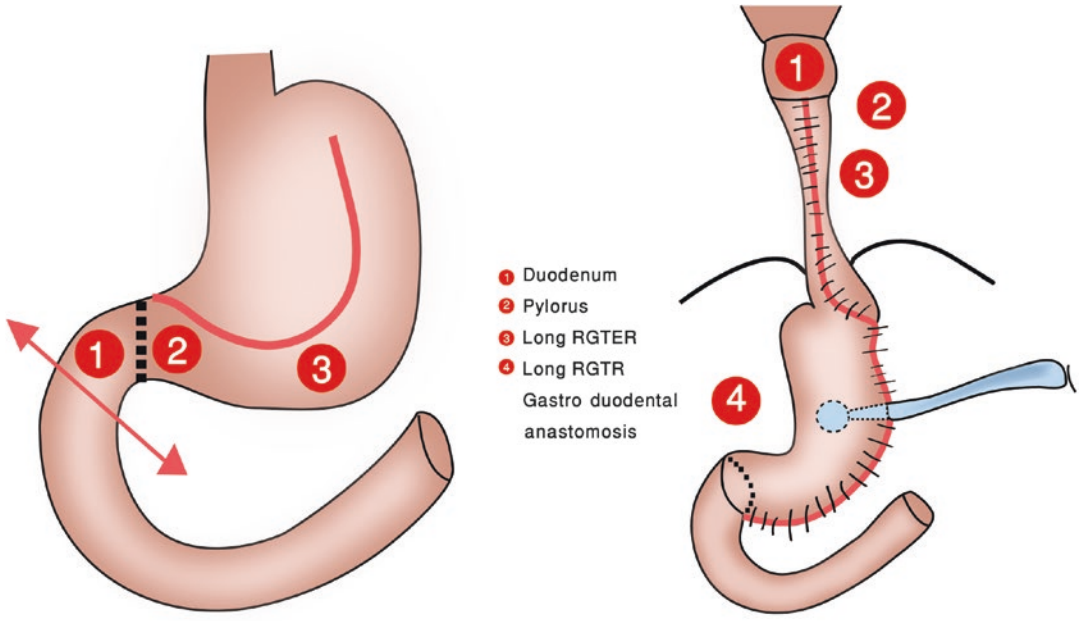

Fig. 29.16 Configuration of the duodeno-gastric tube for pharyngo-oesophageal replacement (Illustrated by M. Hassanieh)

benefit. As the patient is intubated via tracheostomy, the surgeon has free access to the mouth which can facilitate anastomosis.

Oral rehabilitation takes time and should involve a speech therapist.

In all three of our patients, the post-operative video fluoroscopy showed that the pylorus, which was in the position of a pharyngo-oesophageal sphincter, maintained its original function and opened intermittently. Perhaps in these patients an extra-mucosal pyloromyotomy might have been of value. In each of our patients, oral feeding for liquids and solids was established, but this took up to 2.5 months of intensive rehabilitation. Two patients had excellent long-term results, whilst one died in obscure conditions 2.5 years after surgery due to complications of his tracheostomy.

Laparoscopic Surgery for Oesophageal Replacement

With the recent tremendous popularity of laparoscopy in all fields of surgery, its application to oesophageal replacement is hardly surprising. Since 2007, there are four reports of laparoscopic-assisted oesophageal replacement in children with oesophageal atresia and caustic injuries. In seven patients (four EALG and three caustic strictures), the whole gastric conduit transversed the posterior mediastinum [23, 24]. Pyloroplasty was done laparoscopically, but open neck anastomosis was performed. In two patients with caustic strictures, the oesophagectomy was performed thoracoscopically in one and by open thoracotomy in the other. In two patients with oesophageal atresia, the entire procedure was performed transabdominally [26] with creation of the posterior mediastinal tunnel being performed laparoscopically in one and by thoracoscopic guidance in the second.

Esteves from Brazil [25] published his experience in five patients in whom oesophagectomy and colonic interposition was performed entirely laparoscopically. These interesting experiences should be viewed as successful case reports. There is no significant advantage in terms of early or late complications or on the early or late post-operative course of patients following the laparoscopic approach.

Although there has not yet been a report of a true reversed gastric tube oesophageal replacement being performed entirely laparoscopically, experience with the very similar bariatric sleeve procedure used to manage obesity in children suggests that it will be soon forthcoming. However, all laparoscopic techniques, though seductive and modern, should demonstrate real advantages over the open procedure before being universally adopted.

Post-operative Course and Complications of Reversed Gastric Tube Replacement

Initial Post-operative Care

The great advantage of the gastric tube is its excellent blood supply and the low risk of sepsis. In our experience of 109 patients over a 34-year period (1975–2009), 50 % of the patients had an uneventful post-operative course. Patients were admitted to the ICU for 1–3 days, but ventilatory support was for a short period only (12–24 h). Half of the patients were extubated at the end of the operation in the operating room. There was no need for post-operative parenteral nutritional support.

Generally speaking, broad-spectrum antibiotics are given for 2–4 days intravenously; however, there are no prospective studies that confirm the need or efficacy of this policy. Pharyngeal suction is frequently necessary during the early post-operative period but may be avoidable in patients with a gastric tube in the posterior mediastinum. In patients in whom the gastric tube is placed retrosternally, pharyngeal suction must be continued for 2–5 days and should be continuous.

The "J" vacuum drain is removed when nothing has drained for 24 h. This is usually after 2–5 days. Enteral feeding via gastrostomy is introduced as soon as bowel function has restored.

In patients, who have an uneventful post-operative course, the integrity of the gastric tube can be simply checked at the bedside by giving the patient a coloured cool drink to swallow. This should flow quickly and easily out through the gastrostomy tube. Some surgeons prefer to request a contrast swallow under fluoroscopy.

Oral liquids, then a soft diet are introduced progressively until normal feeding for age is reached, usually around day 14–21 postoperatively. The gastrostomy is kept for 2–3 months in case a late stricture of the upper anastomosis requires intervention.

In children with serious co-morbid conditions, oral feeding can be delayed for weeks or months despite intensive speech therapy.

After gastric tube oesophageal replacement, the risk of progressive narrowing of the cervical anastomosis mandates regular follow-up. Routine post-operative dilatations are not recommended. Follow-up by clinical examination, video-recorded contrast swallow and endoscopy should be carried out monthly for the first 6 months to identify early stricture formation that may require dilatation. In our experience, 40 % of the patients had between one and six post-operative dilatations of the cervical anastomosis. Dilatations should preferably be performed with balloon dilators or over a guide wire. Long-term follow-up is essential for all patients having oesophageal replacement and this is the main topic of the second chapter on oesophageal replacement.

Early Post-operative Complications

Cervical Anastomotic Stricture

Fistulation at the oesophago-gastric anastomosis is the most common complication of gastric tube oesophageal replacement (Fig. 29.17). The frequency in large series (both gastric tube and colonic interposition) ranges from as high as 66 % [43] to 13 % in our experience with a mean of 50 %.

Anastomotic leaks vary in severity from minor leaks that close spontaneously within 10–14 days without stenosis to complete anastomotic disruption due to ischaemia at the cervical end of the gastric tube. Fistulae are more common after retrosternally sited tubes than posterior mediastinal tubes. In our experience, fistulae arose in 7 of 19 retrosternal tubes (37 %) and in 8 of 90 (7 %) posterior mediastinal tubes. There

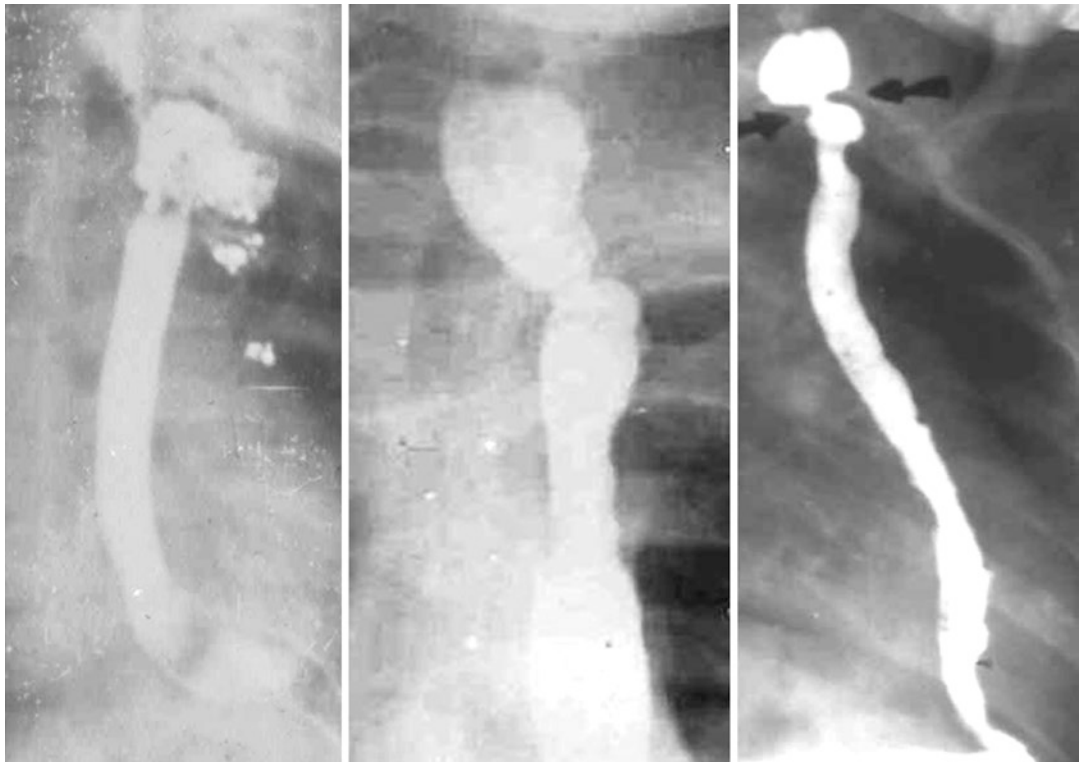

Fig. 29.17 X-ray of common complications of cervical anastomosis: fistula, mild or severe stenosis

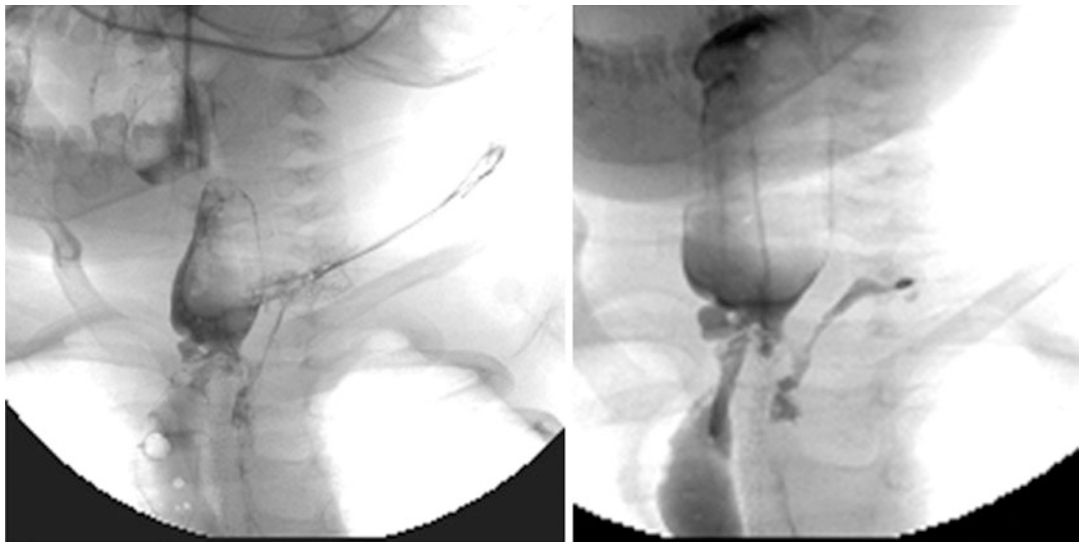

Fig. 29.18 Fistula of cervical anastomosis on post-operative day 6 with spontaneous closure in 14 days

is no clear explanation for the difference, but perhaps the shorter tube and fewer angulations of the mediastinal route represent contributing factors. Following a fistula, a stenosis must be expected, and these patients should be followed closely with regular contrast studies and have early dilatation if necessary (Figs. 29.18, 29.19, and 29.20).

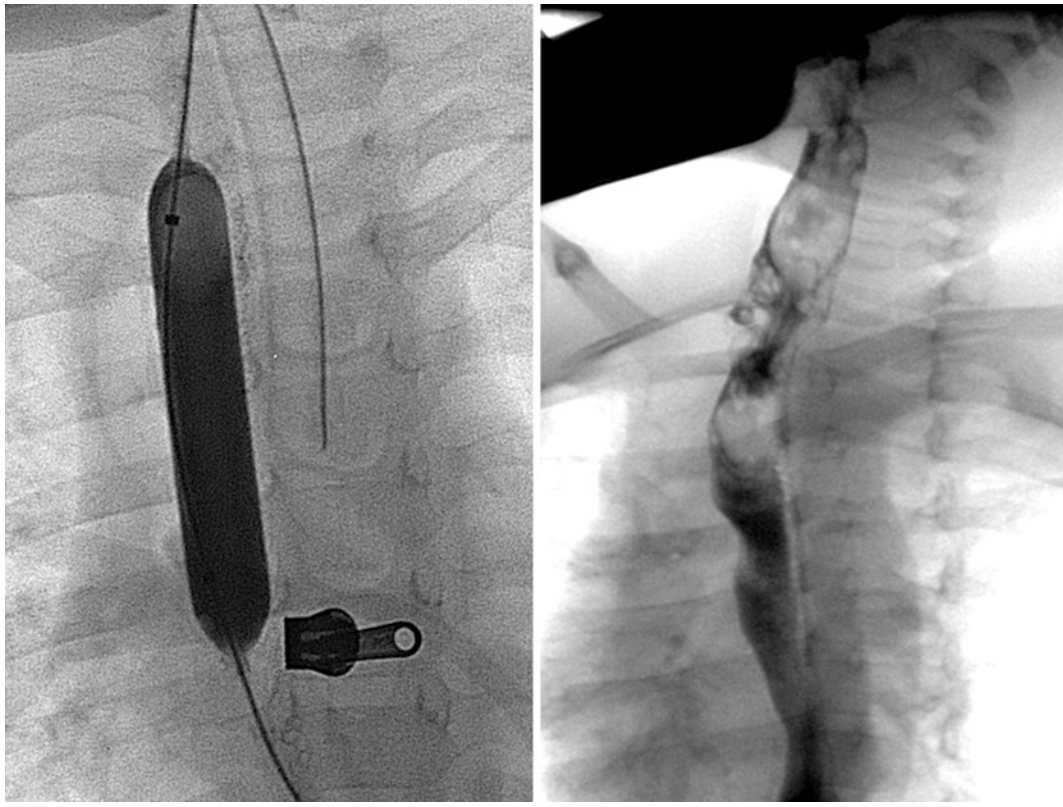

Fig. 29.19 Same case as Fig. 29.18. with balloon dilatation of the stricture day 28 postoperatively

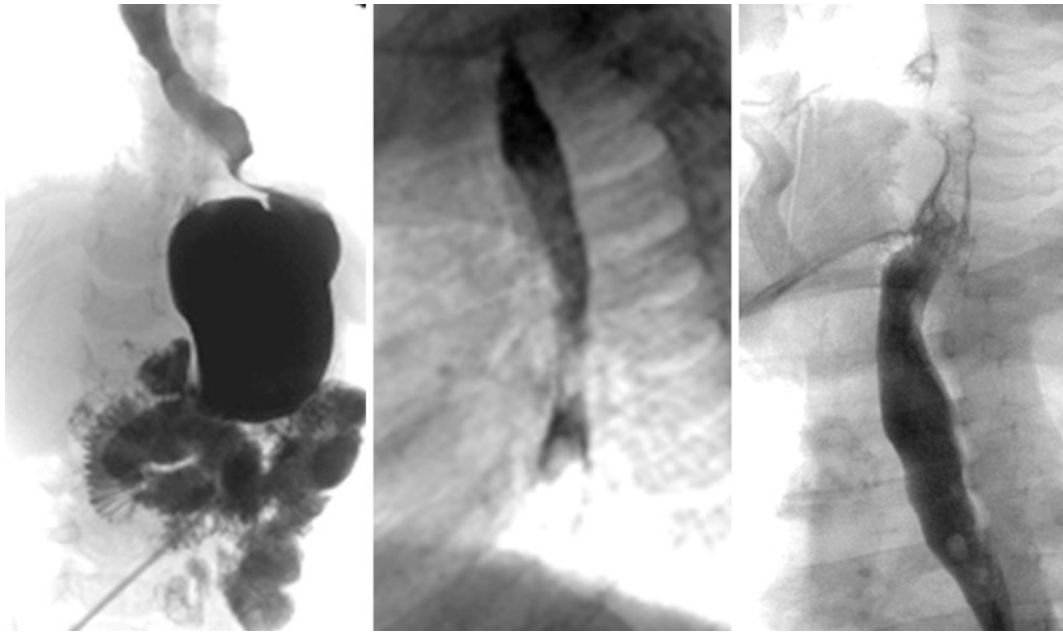

Fig. 29.20 Same case: very good result 6 months later; normal oral feeding, good volume of the gastric reservoir

A well-perfused gastric tube created with surgical precision and the placement of the tube in the posterior mediastinal position have allowed us to reduce our incidence of these complications from 37 to 6 % with a mean of 13 % in our 109 patients.

Post-operative Mediastinitis

This is a serious challenge in the early post-operative period and the viability of the graft should be confirmed without delay. Whilst imaging may be helpful, surgical re-exploration is the safest way to confirm gastric tube viability.

Mediastinitis is heralded by the sudden onset of clinical sepsis, often presenting with septic shock, and the chest X-ray may demonstrate a pneumo-mediastinum with or without a pleural effusion. Despite early drainage, aggressive antibiotic therapy and full supportive measures mortality are frequent. The most frequent underlying cause is a leak from the long suture line, and when this is performed with a stapler without oversewing, the risk is high. Newer stapling devices closing the tube with three layers of staples may further minimize this complication. No intraperitoneal sepsis occurred in our patients.

Necrosis of the Gastric Tube

This is a rare but potentially life-threatening complication. The cause is always vascular and most frequently results from the stubborn decision of the surgeon to persist with a tube that is blue and with poor bleeding when it is brought to the neck. The only treatment is emergency removal of the necrotic graft. All attempts to salvage a compromised gastric tube will end in failure.

When the gastric tube is in the mediastinal position, severe mediastinitis accompanies graft necrosis and may result, as in one of our patients, in death.

Removal of an ischemic tube will need to be followed by a new substitute (colon or jejunum) placed retrosternally after a delay of several months. The problems of failed oesophageal replacement have been the subject of several papers [30, 49].

Conclusion

Our experience after 34 years of oesophageal replacement (1975–2009) includes 109 gastric tubes (the first 19 retrosternal and the remainder sited in the posterior mediastinum), in addition to 37 colonic interpositions using the transverse colon in 35 and the left colon in two. Colonic interpositions were placed retrosternally in 29 patients and transmediastinal in 8.

The advantages of a reversed gastric tube oesophageal replacement as a one-stage procedure without thoracotomy and with placement of the tube in the posterior mediastinum can be summarized as such:

1. The gastric tube has an excellent blood supply.
2. Due to acid secretion, there is a low risk of sepsis.
3. The operative procedure is straightforward when performed by an experienced surgeon and made safer and quicker by the use of stapling devices.
4. The gastric reservoir as well as gastric and pyloric function is fully preserved.
5. Performed by an experienced team, the operation has a low morbidity and mortality.

However critics would present the following arguments:

6. After gastric tube creation, the stomach is of small capacity.
7. Gastric tube creation could induce megaloblastic anemia resistant to treatment.
8. There have been reports of Barrett's oesophagus occurring within the cervical oesophagus with a potential for malignant transformation.
9. Some patients could develop post-vagotomy syndromes such as dumping.

These hypothetical disadvantages were not encountered in our experience. Dumping is particularly common after iso-peristaltic gastric tubes, and these are not recommended for this reason. The major problems with reversed gastric tube oesophageal replacement relate to the cervical anastomosis, but with meticulous technique, strict follow-up and early dilatation when necessary these problems can be controlled.

Oesophageal replacement in childhood remains a major operation, which requires expertise, experience, modern technology and a multidisciplinary team working at a specialized centre. Although the total gastric transposition appears a safe procedure and is popular in many countries, it cannot be recommended universally as it inevitably causes complete or partial loss of the gastric reservoir and normal gastric function [94]. From the author's perspective, gastric tube oesophageal replacement and colonic interposition remain the two recommended procedures for children as both preserve gastric reservoir and functions that are essential to normal growth and development [95].

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Colon (Including Ileum) Interposition

30

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and Alaa Fayez Hamza

Introduction

It is a fact that the native esophagus is the best; there is no better substitute for the native esophagus; no ideal graft. In pediatric surgery efforts are not saved to preserve the native esophagus, but reconstruction is considered in cases of failure. Cases that have irreversibly lost their ability to normal oral feeding due to certain esophageal disorders either congenital or acquired are indicated for esophageal replacement. Arguments are still present about the organ used (whole stomach, gastric tube, small bowel, or colon), the route passed from the abdomen to the neck (subcutaneous, retrosternal, transthoracic, or posterior mediastinal), the surgical technique, and the urge to remove the native diseased esophagus. The colon is the most commonly used organ, and experienced centers consider the colon as a good substitute in caustic strictures.

Arul and Parikh [1] defined the requirements for the ideal esophageal substitute. Ideally, esophageal conduit allows normal feeding and functions normally throughout the whole life of the individual. Preferably, the chosen graft permits replacement of the entire esophagus whenever indicated. At the same time, it does not cause respiratory compromise, does not become tortuous or redundant, nor has increased risk of malignancy. Gastroesophageal reflux in the conduit should be minimal. The procedure should be technically adaptable for small children, and replacement results should be reproducible by different surgeons.

Over the last 40 years, more than 1,000 cases of esophageal replacements were done in the Pediatric Surgery Department, Ain Shams University. The technique has been evolved from gastric pull-up to colon replacement, initially subcutaneously and then retrosternally. We used the left colon in all cases since 1972. In the last 22 years, we started transhiatal esophagectomy with posterior mediastinal colon interposition.

History of Esophageal Replacement

The importance of the esophagus is invaluable to everyday life and health. Swallowing food is a process that is fundamental to life. Dysphagia interferes with the basic body needs of nutrition and hence requires to be remedied at the earliest [2]. The sentence "He who cannot take part in the friendly meal is half cut off from the society of man," which is quoted by Myers [3] from Thomson [4] who, in 1878, wrote an article entitled "Notes on gastrostomy in stricture of the esophagus with report of a successful case by Professor F. Trendelenburg of Rostock," was used by Myers as the theme of his article which

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was based on the 25th Herbert Michael Moran [5] Lecture in Medical History.

The greater part of the history of esophageal replacement relates to the management of carcinoma of the esophagus. The first attempt for esophageal reconstruction was done by Bircher [6] in 1894, when he used a skin tube. Since then, many methods for esophageal replacement have been developed.

Esophageal replacement in children was not employed until the second half of the twentieth century when it was introduced for the treatment of various types of esophageal atresia, particularly those with long gap between the two ends [7]. Before that, patients in whom esophageal continuity could not be restored were treated with cervical esophagostomy (spit fistula) and gastrostomy. Later on, connection was accomplished by a rubber tube passing from the cervical esophagostomy to the gastrostomy stoma [8]. The next step was the formation of a skin tube down the anterior chest wall, which was unsatisfactory for a variety of reasons including esthetics and development of malignancy [9].

Historically and till now, colon replacement continues to be the most preferred widely used procedure for esophageal replacement in children. In 1921, Lundblad [10] reported the first successful colonic bypass in a child 3 years old suffering from caustic esophageal stricture. The patient lived and swallowed normally until his death in a car accident when he was 37 years old. In 1948, Sandblom [11] was the first to use the colon for replacement in esophageal atresia.

In 1951, Rudler and Monod-Broca [12] described the retrosternal ileocolonic graft. In the 1950s, colon replacement became more popular with the availability of antibiotics and better anesthetics. Dale and Sherman [13], in 1955, described two infants with esophageal atresia who had reconstruction of the esophagus at 2 years of age using a right colonic retrogastric anterior mediastinal interposition. Four years later, Battersby and Moore [14] reported five cases of right colon replacement for congenital atresia of the esophagus. They recommended delaying the procedure until the infant was at least 9 months of age. Sherman and Waterston [15] achieved major advances in colonic replacement in 1957. Waterston and coworkers [15, 16] and Belsey [17] used isoperistaltic transverse colon based on the left colic artery via the left transpleural route.

In 1967, Othersen and Clatworthy [18] stated that the colon was the best organ for esophageal replacement in children and recommended delaying the operation until the age of 18–24 months old so that gravity in the erect position would assist in food passage through the transposed colon. In 1981, Rodgers [19] was the first to publish transhiatal esophagectomy in children, and he replaced the esophagus with right colon retrosternally. Freeman and Cass [20], in 1982, preferred placing the colon in the route of the native esophagus in the posterior mediastinum and reported an impressively low rate of complications.

Evaluation and Indications

There are two main indications for esophageal replacement: long-gap esophageal atresia and undilatable caustic esophageal strictures or that is resistant to frequent dilatation sessions. Recently, the needs for esophageal replacement in pediatric surgical practice have been decreased. This decrease owes to the improvements that have occurred in the management of esophageal atresia leading to only minority of cases where esophageal continuity cannot be restored and the recent advances in nonsurgical management of caustic esophageal strictures, e.g., topical mitomycin C application that has improved the results of endoscopic dilatation. Failed esophageal surgery (e.g., congenital stricture) represents another indication for esophageal replacement. Other rare indications include tumors, epidermolysis bullosa, and extensive intractable reflux strictures.

Children younger than 5 years old represent the most vulnerable group for accidental caustic ingestion with incidence peaks at around the age of 2 years when children develop skills of localization but are poor discriminators between the harmless and harmful substances [21].

Corrosive injury usually causes dense cicatrization of the esophageal wall that results in rigid strictures that are difficult to dilate [22]. The degree and the extent of a corrosive lesion depend on the characteristics of the caustic agents (concentration and pH), the amount ingested, and duration of contact of the corrosive agent with the esophageal wall [23, 24]. Most caustic esophageal burns are caused by alkalis. Alkalis ingestion causes liquefactive necrosis with deeper penetration, while acidic substances tend to cause a coagulative necrosis of the mucosa, and the resultant eschar formation tends to limit penetration and the subsequent injury to esophagus [21].

The management of some patients with caustic esophageal stricture is challenging and time consuming. This mostly related to the extent and the depth of fibrotic reaction. Stricture recurrence after initial dilatation is frequent, especially in patients who have severe, long, and tight strictures at presentation that eventually necessitate substitution [25]. A period of 8–12 months of regular dilatation is enough to determine the need for surgery in most cases. Other indications for replacement in caustic patients include multiple extensive strictures, marked irregularity or pocketing of the esophagus, and the presence of tracheoesophageal fistula [26].

Replacement in cases of esophageal atresia is indicated in patients with wide gap esophageal atresia (more than three to four vertebrae) with or without fistula, birth weight less than 1,500 g, prematurity and respiratory distress hindering thoracotomy, major cardiac anomalies, and late presenting cases (after 5–7 days) suffering from sepsis and major chest problems (e.g., pneumonia), patients with major leakage after repair, those with disruption of the anastomosis and recurrence of fistula, or those with severe anastomotic stricture unresponsive to endoscopic dilatation.

Although the choice of a proper conduit for esophageal replacement is controversial and reflects the surgeon's preferences and experience, esophageal replacement with or without esophagectomy is a major surgical demand. Each known procedure has its own advantages and disadvantages [27]. Essentially, the substitution needs to function as an efficient conduit to satisfy the nutritional needs and should continue to grow with the child. Our center shares the view of many investigators [28–32], that an isoperistaltic left colon segment based on the left colic vessels is the preferred graft for esophageal substitution. We used to pass the graft from the abdomen to the neck within a retrosternal tunnel or through the posterior mediastinum.

Patients with caustic injury who are able to swallow and those with acceptable weight gain are prepared for surgery without a feeding gastrostomy. Otherwise, a Stamm gastrostomy is an essential preparatory step to improve weight gain which is an important factor contributing to postoperative healing and decrease incidence of leakage and dehiscence.

Patients with esophagostomy (spit fistula) in cases of long gap or failed esophageal atresia repair are encouraged to swallow (sham feeding); otherwise, feeding difficulties are encountered after colon replacement. Reconstruction in those patients is usually planned at age of 6–9 months after gaining acceptable weight.

Operative Technique

Preoperative Management

The site of the stricture is very important to have an idea about the location of the proximal anastomosis and the presence of healthy mucosa proximal to the site of the stricture should be confirmed. If the barium swallow is not conclusive, then on table, upper endoscopy can locate exactly the site of proximal stricture and the healthy mucosa proximal to it, where the coloesophageal anastomosis will be constructed.

Patients are admitted 2 days before surgery for routine laboratory and radiologic evaluation (only chest x-ray usually). Patients who can swallow are given clear fluids 48 h preoperatively and to be NPO over the night of surgery, when full maintenance intravenous fluids are started. Colonic washouts (enemas) with 20 ml/kg body weight are done every 8 h 48 h before surgery, to be increased every 6 h the day before surgery.

Those with a gastrostomy tube have Ringer's solution infusion through the tube with 10 ml/kg body weight over 15–20 min. This is repeated for another three times every 2 h in the night before surgery. All patients are given intestinal oral antiseptics 3 days before surgery (metronidazole and colimycin). The day of surgery, intravenous cephalosporin and metronidazole are given 2 h before operation.

Operative Technique "Isoperitaltic Left Colonic Graft"

Position and Sterilization The patient is put in the supine position with a pillow below his shoulders, and the head is tilted to the right side (Fig. 30.1). Preparation by povidone-iodine (in cases with no allergy to iodine) should include the whole body and the neck; drapes should expose the operative field, and both chest fields in case of emergency thoracotomy are needed. The anesthetist should put a rigid tube through the nose in the esophagus till it stops which is the location of proximal stricture. This helps during dissection of the esophagus especially in severely injured patients. Surgeons could be divided into two teams to decrease operative time (neck team and abdomen team).

The Neck After positioning the tube in the esophagus, left transverse supraclavicular incision is made (Fig. 30.2), which can be extended upward in a hockey stick manner over the anterior border of the sternomastoid. Division of the strap muscles makes dissection easier. Isolation of the esophagus is done after identification of the recurrent laryngeal nerve. Dissection of the esophagus (Fig. 30.3) should be done carefully to avoid injury of the blood supply. Distal dissection around the esophagus is usually done bluntly

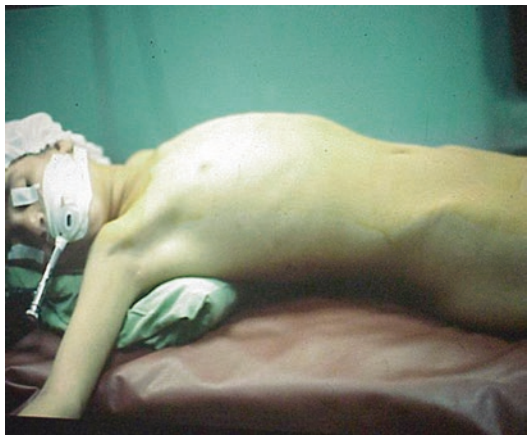

Fig. 30.1 Position of the patient

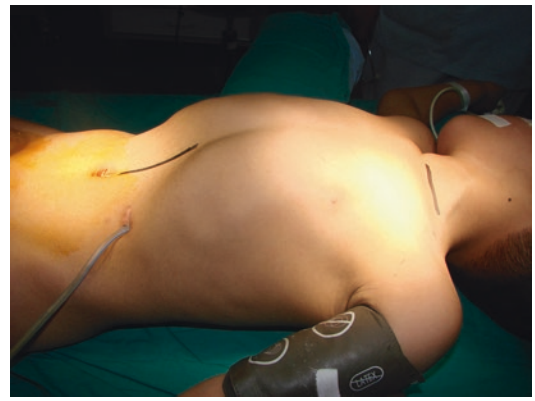

Fig. 30.2 Abdominal and neck incisions

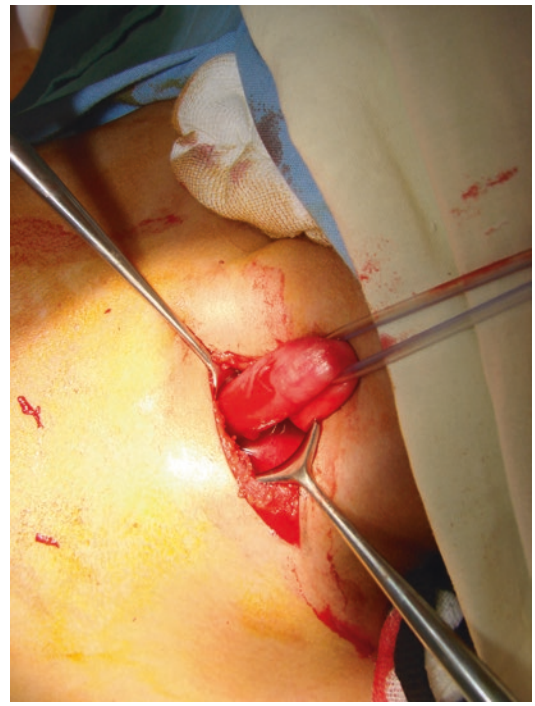

Fig. 30.3 Neck dissection of the upper esophagus

through the posterior mediastinum. Proximal dissection should extend up until normal pliable esophagus with healthy looking is reached. In cases of pharyngeal strictures, higher dissection is needed and the incision should be extended to the angle of the mandible. Cutting through the pharyngeal muscles is done, and stay sutures are taken on the wall of the pharynx before incising it with the help of an intraoral instrument or a finger of the assistant. Anastomosis is usually done at the level of the pyriform sinus. When the neck is ready, then both teams are joined together to pull the colon through:

- Note: incoordination and swallowing problems are present in all patients suffering pharyngeal strictures; however, most of them show variable degrees of gradual improvement. The sensory and motor functions of the pharyngeal tube are affected due to the direct corrosive damage of the pharyngeal wall mucosa and muscles. Incoordination and swallowing problems vary according to the severity of injury and the age of the child. Younger children may suffer more as their pharyngeal tube is narrow with low total surface area. The corrosive pharyngeal injuries may also affect severely the larynx up to suffocation, necessitating tracheostomy. In addition, loss of sensation in the hypopharynx and supraglottic larynx plays a major role in the development of aspiration observed in those patients.

Dissection of the Colon The abdomen is entered through a midline incision (Fig. 30.2), and usually some adhesions are encountered in cases of previous gastrostomy, but this is much avoided with the use of laparoscopic gastrostomy. Mobilization of the colon is done, with careful dissection and avoiding any hematoma or injury to the vessels. The graft is chosen on the territory supplied by the ascending left colic artery (Fig. 30.4), and the graft length is measured from the site of the healthy part of the esophagus to the site of anastomosis on the stomach. We usually ligate the middle colic artery to have a good length, but if there are any vascular anomalies, the right or even the middle colic artery is utilized. After choosing the colonic graft, bulldogs clamp the blood supply, and the colon is left inside the abdomen to verify adequate circulation (Fig. 30.5). The colon is reevaluated and resected at the proximal end (right side) of the colon only after verification of its vascularity and length. The graft is washed with diluted povidone-iodine solution with an intestinal clamp on the distal part to wash only the desired segment, and then it is passed behind the stomach through the gastrohepatic ligament in an isoperistaltic manner. To facilitate passage through the chest, a silk suture is applied to the proximal end of the colon and pulled through the cervical

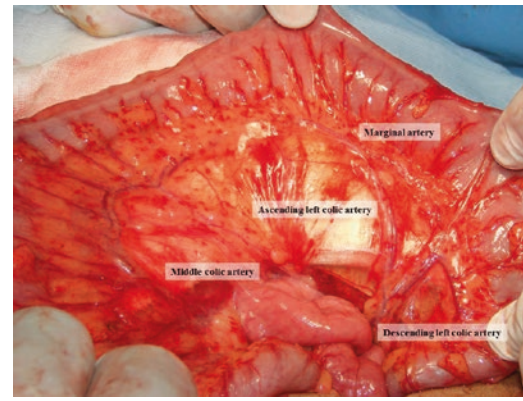

Fig. 30.4 Vascularity of the left colon graft

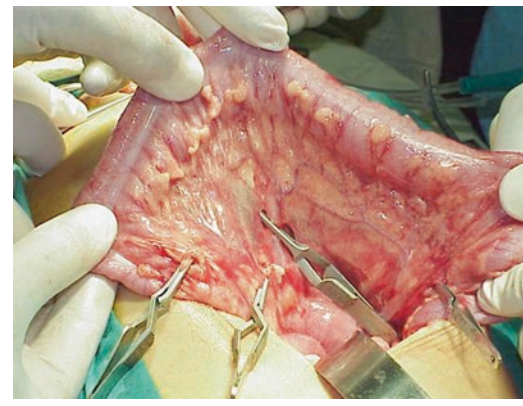

Fig. 30.5 Evaluation of the vascular pedicle

incision until the colon is in place, either in the tunnel retrosternally or in the posterior mediastinum. To avoid redundancy, the proximal anastomosis is done first before resecting the distal part of the colon.

Retrosternal Colon Bypass Dividing the endothoracic fascia very close to the sternum makes a wide retrosternal tunnel (Fig. 30.6); blunt dissection is done carefully to avoid pleural injury. Suprasternal dissection is important, and the tunnel should be widened with the fingers from above and below to avoid colonic obstruction especially at the suprasternal notch. A long clamp is passed from the lower edge to the suprasternal notch and a catheter is grasped by the clamp, then it is pulled through the tunnel, the silk stitch of the proximal part of the colon is sutured to the catheter, and the colon is pulled through the tunnel with no rotation. In order to avoid redundancy, we measure accurately the colon and resect exactly the length needed before anastomosing the distal end in a simple two-layer anastomosis. Cologastric anastomosis is done to the anterior wall of the stomach with U-shaped stitches (similar to Belsey Mark procedure). As the colonic graft lies close to the inferior border of the liver, it could be kinked by it especially in the standing position; therefore, the inferior border of the liver is fixed to the diaphragm and/or to the anterior abdominal wall.

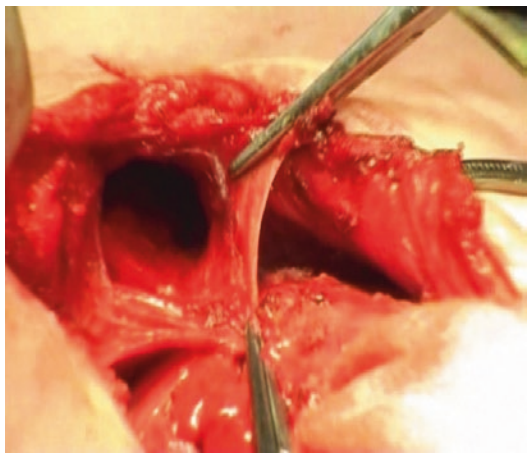

Fig. 30.6 Wide retrosternal tunnel

Transhiatal Esophagectomy In posterior mediastinal colonic replacement, the esophagectomy is done by cutting the left triangular ligament of the liver followed by dissection of the esophagus after encircling it with a tape. After freeing the esophagus from all its attachments, the esophageal hiatus is explored by dissection with the help of retractors inside the hiatus. With direct vision, all esophageal vessels are secured by diathermy (Fig. 30.7a, b), so there should not be fear of blood loss or damaging vital structures around the thoracic esophagus. Direct vision is ensured by retractors inside the hiatus and applying alternate traction on the esophagus. Running dissection strictly close to the esophageal wall is another safety factor during removal of a severely injured esophagus with dense periesophagitis.

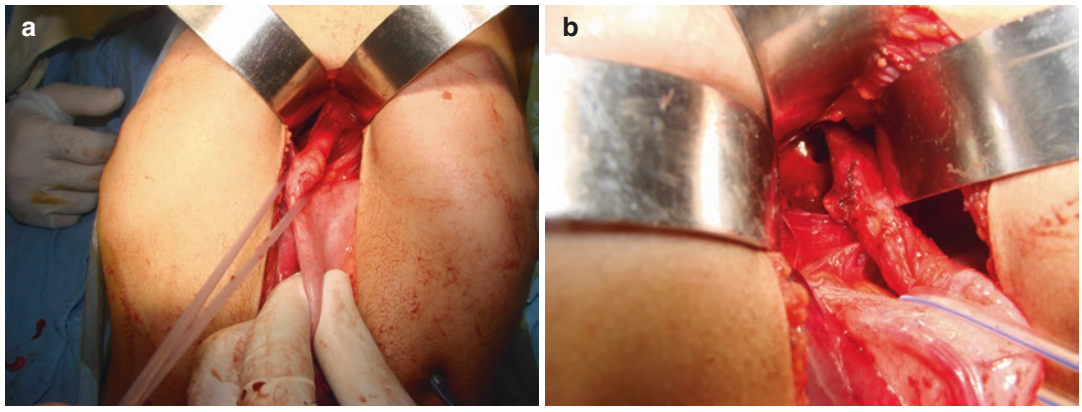

Fig. 30.7 (**a**, **b**) Transhiatal esophagectomy

With blunt and sharp dissection, the esophagus is freed as high as possible, often higher than the pulmonary ligaments. Care is taken to avoid entering the pleura, or an intercostal tube drain has to be inserted. Blunt finger dissection of the esophagus is carried on from above and below until the dissection is complete (fingers of both hands touch each other) (Fig. 30.8). The esophagectomy then is done by cutting the esophagus at the cardia; the esophagus then is pulled from neck incision after suturing a long silk stitch to the esophageal end. The silk is sutured to the proximal end of the colon and pulled through the posterior mediastinum and out of the cervical incision:

- Note: transhiatal route is direct and is the shortest route an esophageal substitute can traverse between the neck and abdomen. It permits removal of the scarred esophagus (Fig. 30.9), which has a definite increased risk of malignant changes, cyst formation, and empyema if left in place.

A single layer end-to-end esophagocolic anastomosis is done by the cervical team; in some cases, end to side is done if there is discrepancy between colonic and esophageal ends. In fixation of the colon to the neck muscles, the incision is closed after a drain is placed.

The colon is now accurately measured, and distal resection is done exactly with no extra length. Great care should be taken at this step not to affect the continuity of the distal marginal arcade. Gastrocolic anastomosis is performed at the cardia with an antireflux wrap of the stomach 270° (Fig. 30.10a, b) to avoid compression of the blood supply. Pyloroplasty is done in most of the cases, and the colon is fixed to the edge of the hiatus:

- Note: vagotomy done in association with esophagectomy helps reduction of symptomatic gastrocolic reflux and peptic ulceration of the colonic graft as it reduces gastric acidity and eliminates reflux symptoms. The accompanying pyloroplasty aggravates this effect as it promotes gastric emptying.

Stamm gastrostomy is fashioned for patients who underwent replacement without a preinserted gastrostomy tube. The colonic continuity is restored, mediastinal drain is inserted, and the abdomen is closed. On table fluoroscopy is done for exclusion of iatrogenic pneumothorax. If pleural injury is found, a chest tube is inserted immediately.

Postoperative Management

Patients usually stay in the intensive care unit for 2–4 days because occasionally, postoperative ventilation is needed. The tube drains are removed after 48 h, and patients are kept on nothing per mouth status (fed by the gastrostomy on the fourth day) for 7–10 days; oral feeding is then

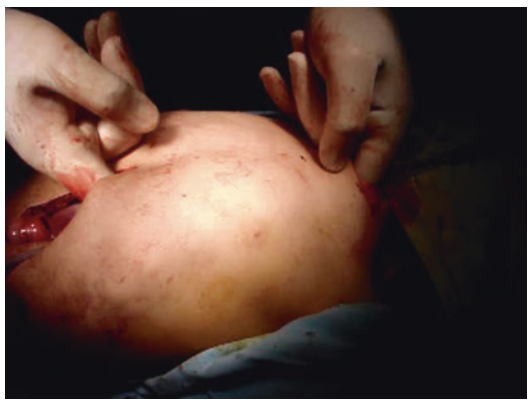

Fig. 30.8 Blunt finger dissection of the esophagus

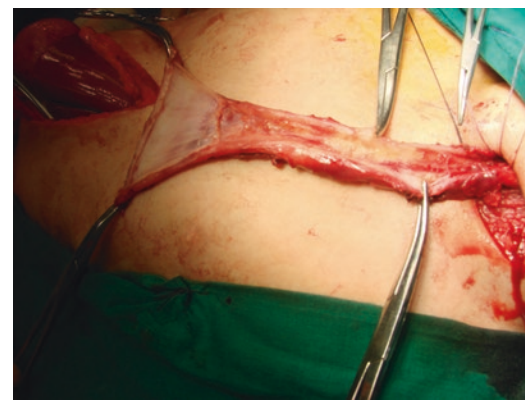

Fig. 30.9 Scarred esophagus due to caustic ingestion

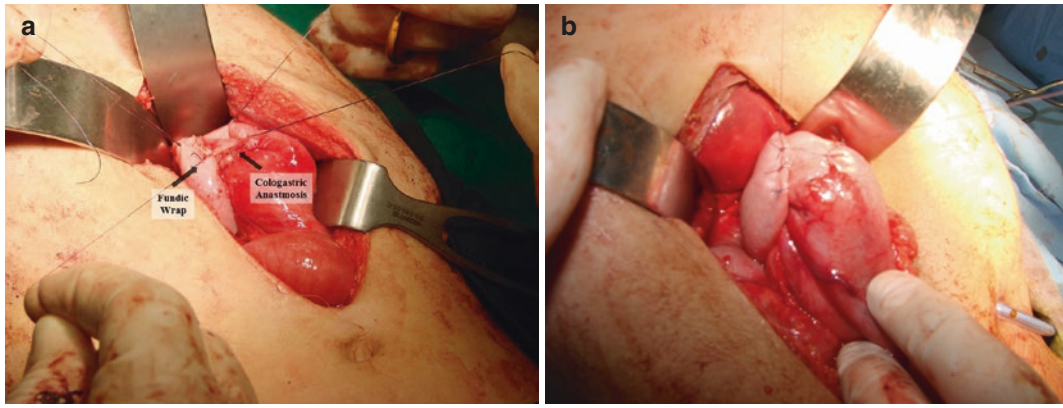

Fig. 30.10 (**a**, **b**) Antireflux 270° wrap around the cologastric anastomosis

started. A contrast study is not routinely necessary. Gastrostomy tube is usually removed after 3 months of being not used. If there is leakage from the cervical anastomosis, it usually stops spontaneously; oral feeding can be started after leakage ceases.

Most of the cases will be discharged after 10–12 days after resuming oral feeding with supplemented gastrostomy feeding till complete oral diet:

- Note: although utilizing the colon as a graft for esophageal replacement is a relative easy technique to perform, three anastomoses should be performed, namely, esophago- or pharyngocolic, gastrocolic, and colocolic.

Surgical Tips

How to avoid ischemia of the graft:

- Double blood supply; the left colic and marginal paracolic arcades vessels [33].
- Ligation of the middle colic artery during the gastrostomy procedure helps to improve the vascularity in the marginal arcades [34], provided that there are no vascular anomalies of the left colon.
- Ensure adequate venous drainage.
- Avoid tethering of the graft pedicle by the descending branch of the left colic artery and the descending colon by resecting about 5–10 cm of the colon just distal to the graft without affecting the marginal arcade by division of the small end vessels [33, 35].
- Ensure adequate width of the passage traversed by the graft to and from the thoracic cavity, especially in the retrosternal route, to avoid the potential for graft compression that may lead to ischemia.
- Avoid torsion of the graft during its passage to the neck.
- Mind tension-free, straight graft.
- 270° antireflux wrap is better for blood supply than 360° wrap.

How to avoid redundancy of the graft:

- Accurate measurement of the graft length
- Resection of the distal part (left side) of the colon after esophagocolic anastomosis and fixation of the colon to the neck muscles

How to prevent esophagocolic anastomosis leakage and strictures (should be 0% in the atresia patients):

- Very careful dissection of the esophagus.
- Tension-free anastomosis.
- In cases of scarred esophagus, esophagocolic anastomosis should be performed in an area lined by healthy esophageal mucosa.

How to avoid gastrocolic reflux:

- 270° wrap.
- Isoperistaltic colon graft.

- It is of value to mention that Jones et al. [36] and coworkers performed a study on nine adult patients underwent left colon interposition for benign esophageal strictures. The cologastric anastomosis was held in the posterior wall of the stomach at the junction of its proximal and middle third. When they experimentally stimulated the colonic graft with acid, the graft responded by reproducible colonic contraction which is comparable to the type II colonic contraction described for the colon in normal position. Also, they measured the resting supradiaphragmatic colonic pH. They proposed that interpositioned colon acts as a protective barrier between the stomach and the proximal esophagus, and any acid reflux is either buffered immediately by alkaline colonic secretions or induces colonic peristalsis with eventual return of the acid into the stomach. This proposal augments the role of isoperistaltic colon graft in preventing symptomatic gastrocolic reflux.

Advantages and Disadvantages of the Transhiatal Route

- More anatomical, straight, shortest distance to the neck, easy to do antireflux, and allows direct anastomosis to the cardia which is more anatomical and physiological.
- Permits resection of the unused nonfunctioning esophagus, which is important to eliminate the risk of Barrett's esophagus especially in cases of reflux esophagitis. Also, removal of the closed lower end scarred esophagus prevents possible complications like cyst formation, empyema, or even malignant transformation.
- The presence of the colon graft in the posterior mediastinum reduces the incidence of its progressive dilatation and hence protects both lungs from compression [31].
- Allows straight nonredundant graft with better functional results.
- On the other hand, the transhiatal route is more difficult, and its operative time is longer than retrosternal route. Also, its morbidity rate is higher especially pneumothorax.

Right Colon

In our series, we used the right colon in one occasion. It was a redo surgery after stenosis of the first left colon graft due to chronic ischemia.

Appignani et al. [30] and his colleagues used the right transverse colon, based on the middle colic artery, eight times in their series. Their indications to use the right transverse colon were redo surgery or unreliable left colic vasculature. The graft was placed in the isoperistaltic direction in all cases:

- Note: the left colon is less bulky and thinner than the right colon. Also, it has a more constant blood supply, which is rarely prone to anatomical variations. In their series, Bothereau [37] and coworkers could not perform right coloplasty after total esophagogastrectomy in 10 patients out of 81 patients (12%) due to insufficient blood supply, poor or missing right marginal artery, or venous stasis.

Results

Over the last 40 years, 965 colon interpositions for 963 patients (two redo cases) had been performed at the Pediatric Surgery Department, Ain Shams University. The indications for surgery were caustic esophageal injury in 849 patients and esophageal atresia in 116 patients. Transhiatal esophagectomy with colon interposition (Fig. 30.11) was performed in 395 patients, and retrosternal colon bypass (Fig. 30.12) was performed in 570 patients. The fact that various surgical procedures are accepted as esophageal replacements means that none of them is the ideal; all have their complications that may be in common or specific for each procedure type.

Intraoperative Complications

Pneumothorax either unilateral or bilateral occurred in 15% of patients, with higher incidence in the transhiatal approach (22%) as compared to the retrosternal route (10%). Intraoperative fluoroscopy (if available) or immediate postoperative

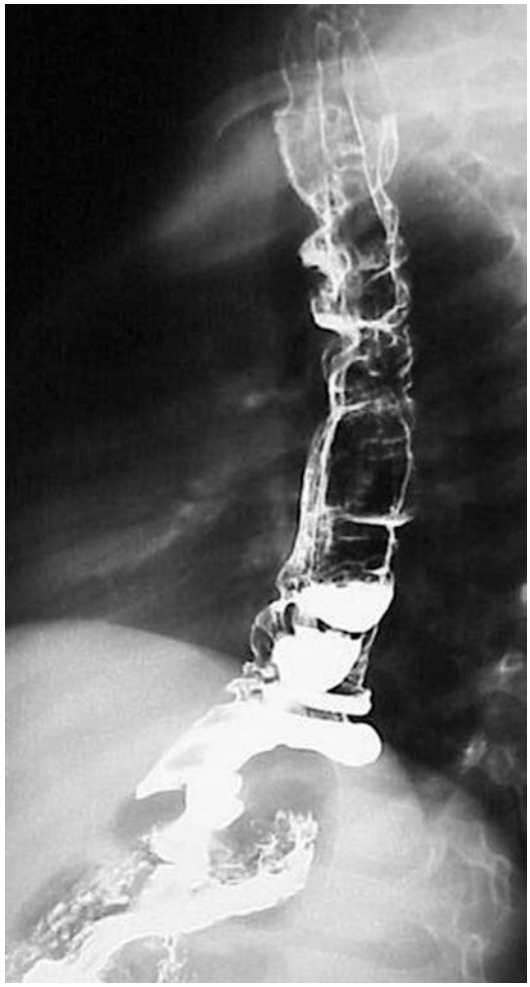

Fig. 30.11 Barium swallow and meal for a child 5 years post-transhiatal colon interposition

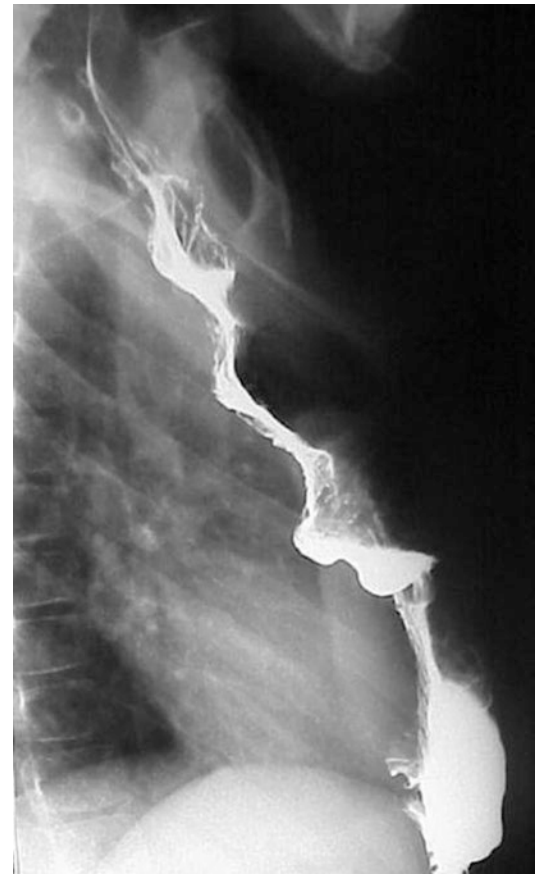

Fig. 30.12 Barium swallow and meal for a child 10 years post-retrosternal colon bypass

chest x-ray should be done in all cases. If there is a pleural tear, an intercostal tube is inserted under water seal till complete lung inflation followed by clamping the tube before its secure removal. Intraoperative tracheal injury occurred in three patients that had previous dilatation injury in our early experience. Major intrathoracic bleeding developed in another patient. All four patients underwent thoracotomy with successful control of the injury.

Postoperative Complications

The most common complication encountered postoperatively is leakage from the cervical anastomosis that occurred in 10 % of patients which is manifested as salivary fistula; all of them resolved nonoperatively within 1–3 weeks. Thereafter almost half of them developed stricture of the cervical anastomosis with varying degrees of dysphagia. These strictures were managed initially by endoscopic dilatation at 3-week intervals, and ten patients required surgical revision of the anastomosis after failure to respond to three sessions of dilatation. Leakage and stenosis of the esophagocolic anastomosis can be avoided by careful dissection of the esophagus avoiding injury to its blood supply and performing a wide anastomosis. The incidence of leakage should be extremely low when the proximal esophagus is healthy, i.e., anastomosis done in an area occupied by healthy esophageal mucosa.

Ischemic necrosis of the colonic graft has an incidence in literature between 3 and 20 % [38].

In our series, no instance of graft necrosis occurred; however, three patients had late graft stenosis (chronic ischemia), two in the distal colonic graft and one in the proximal segment. All three had redo surgery using the right colon in one case, left colon in another one, and gastric pull-up in the third.

The incidence of anastomotic leakage, stricture, and graft necrosis is greatly influenced by the blood supply of the graft. Therefore, using a double blood supply and avoiding any compression or twisting of the graft pedicle must be emphasized, and it should be noted that even minimal twisting that does not impede the arterial supply should be closely evaluated because venous thrombosis is thought to be the usual precipitating factor for graft necrosis, so that great care must be taken to avoid venous drainage impairment as well as the preservation of adequate arterial supply.

We had five patients manifest the effects of recurrent laryngeal nerve injury in the early postoperative period. One of those required tracheostomy. Postoperative bowel obstruction caused by postoperative intussusception, early adhesive intestinal obstruction, or internal herniation of the bowel occurred in 2 % in our series which were managed surgically in most of cases. There were six mortalities (0.6 %) in the early postoperative period owing to respiratory problems and sepsis.

Long-Term Complications

On long-term follow-up, graft redundancy and gastrocolic reflux are the most recognized complications. Redundancy of the interposed colonic graft is one of the late complications that leads to stasis and retention of food and liquid in the graft, causing obstructive symptoms such as dysphagia and regurgitation and increasing the risk of nocturnal aspiration; also redundancy in the chest may decrease the vital lung capacity causing restrictive pulmonary symptoms. In our series, 32 had redundancy, 25 in retrosternal group and 7 in transhiatal group; 6 of them required surgical revision with excision and reanastomosis of the redundant segment of the graft; meticulous dissection is necessary to avoid injury to the mesenteric and marginal vessels supplying the colonic graft.

In long-term follow-up by barium meal, scintigraphy, or pH study, gastrocolic reflux was detected in 22 patients: 18 in retrosternal group and 4 in transhiatal group, 18 of which were asymptomatic. All of those 22 patients were subjected to antireflux measures in the form of antacids and diet modification; only 2 patients needed antireflux procedure.

Chronic exposure of the colonic mucosa to gastric acid may induce ulceration, bleeding, and perforation. Perforation of the colon frequently can lead to empyema; in our series we have only one case of peptic ulceration in the colonic retrosternal graft that was diagnosed endoscopically and managed medically. Colonic mucosa is resistant to peptic ulceration which may be due to its mucus secretion. There are reported cases of malignancy arising in colonic interpositions after esophageal replacements for benign conditions [39–41].

Nishihara et al. indicated that the reconstructed colon had no contractions even after dry swallows [42], while other investigators reported that peristaltic contraction like that of the normally positioned colon was observed after dry or wet swallowing especially acidic swallows [43–45]. However, sufficient stimulus to start colon movement is required; graft distension after successive swallows [43]. Thus, they concluded that most of the time the colon did not show contractions. Generally in colon grafts, these peristaltic waves contribute little to the speed and efficiency of deglutition. Transit and stagnation in the graft are gravity dependent, and the occasional contractions can aid emptying [42, 43]. Manometry cannot always reflect the function of the graft; therefore, controversy still remains regarding the role of the movement in the colon graft. Dòmini [46] and his colleagues reported a case of a female patient, born with long-gap esophageal atresia. She underwent retrosternal substitution using a right transverse antiperistaltic colic segment, when she was 5 months old, but the reversely directed substitute never worked, and the baby was seriously dysphagic and failed to thrive. When she was 11 months old, she was

reoperated. The antiperistaltic colon segment was removed and replaced between the left and right colon; reconstruction was carried out with a retrosternal isoperistaltic ileocecal segment. The baby did well after that, and her problem was resolved.

Colonic grafts used for esophageal replacement seems to act as a barrier between the refluxed gastric acid and the remaining part on the native esophagus, hence protecting the remaining esophagus from developing Barrett's esophagus. The protective value of the colonic graft can be explained by the mucus secreted by the colonic mucosa, which exerts a buffering action against gastric acid. To our knowledge, there are no reported cases of Barrett's esophagus proximal to the esophagocolic anastomosis in cases that underwent esophageal replacement by colon.

Ileal and Ileocolic Grafts as Esophageal Substitutes

In 1991, Mao-Tang Han [47] reported a series of 12 cases that underwent ileocolic replacement of the esophagus through the retrosternal route in an isoperistaltic position. The indication was esophageal stricture secondary to ingestion of caustic fluid in 11 children, while the remaining child was suffering from congenital esophageal stricture. In all patients, the graft "terminal ilium and right colon" was based on the middle colic artery and the marginal arcades. The cologastric anastomosis was made on the anterior wall of the antrum. There was a single mortality on the seventh postoperative day in this series. Small leak occurred from the cervical anastomosis in three children, but it healed spontaneously within 2 weeks without stricture formation. Another child developed slight stricture that responded to dilatation therapy. Redundancy of the graft was found in two patients, however without clinical symptoms. Ten years after replacement, one child suffered massive gastrointestinal bleeding that resolved with antacid therapy without recurrence.

In their published series, Appignani et al. [30] and coworkers used a segment of ileocecum supplied by the ileocolic vessels ten times. They did not use the left transverse colon either due to unreliable left colic vasculature or it was a redo operation.

Bax and Van Renterghem [48] used a terminal ileal graft, 5 cm in length, just proximal to the ileocecal valve to bridge a long gap between upper and lower esophagus in a 10-month-old female infant born with long-gap esophageal atresia with distal fistula. This graft was based on the right branch of the middle colic artery and the vascular arcade of the terminal ilium and ascending colon. The right colon, appendix, and ileocecal valve were sacrificed close to the bowel wall to preserve the blood supply to the terminal ilium and to allow longer mesenteric pedicle to the graft. The graft was passed through the hiatus and transplanted in an isoperistaltic manner. There was a leak from the proximal anastomosis that healed spontaneously, while the distal anastomosis needed to be dilated on a few occasions. Also, contrast showed redundancy of the graft but with good passage. They found that preparing the ileal graft was not difficult, but removing the ileocecal region from the pedicle without interfering with the blood supply was somewhat more difficult. According to experience with children suffering short bowel, they stated that it seems unlikely that removing the right colon and part of the terminal ilium will have a major long-term impact on nutritional status.

- Note: Sonneland et al. [49] and colleagues found that the right colic artery is absent in 12.6 % of 600 examined specimens. In addition, Michels et al. [50] and coworkers stated that the terminal ilium is generally a poorly vascularized area. On the other hand, compromising the terminal ileum and ileocecal valve may affect the nutritional status of the growing child as they lead to impaired vitamin B_{12} absorption [51] and chronic diarrhea [52], respectively.

Conclusion

The cornerstone of a successful esophageal replacement is to fashion a graft with adequate length, is tension-free, and has sufficient blood supply. The colon offers a good substitute to

the esophagus, either in the first surgery or a redo. Although colonic grafts act as a passive conduit, they have acceptable long-term outcome. The colon is the most commonly used organ for esophageal replacement in children worldwide with satisfactory results.

There are different kinds of colonic grafts that can be used to replace the diseased esophagus according to the colonic segment used, the vascular pedicle, the route passed by the graft from the abdomen to the neck, and the peristaltic orientation of the graft. The isoperistaltic left colon graft based on the left colic artery, which passed through the posterior mediastinum, has preferred functional results with straight colon, less redundancy, low reflux rate, and no metabolic disturbances. We believe that using the left colonic graft for replacement of the esophagus through the posterior mediastinum when indicated is the ideal treatment for children with a nonfunctioning esophagus as it can compensate those patients with a near-normal esophagus, i.e., near-ideal graft.

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Esophageal Replacement with Jejunum in Children

31

Klaas(N) M.A. Bax

Introduction

Reconstruction of the esophagus in children, when a larger part of the esophagus is absent or has been destructed, is still a challenge [1–3]. The most important indications for such a reconstruction in children are esophageal atresia (EA, either as a primary reconstruction in pure EA or after failed anastomotic attempts in AE/TEF) or destruction of the esophagus by accidental or suicidal ingestion of a caustic substance. Occasionally a peptic stricture may require esophageal replacement as well. Patients with such indications differ significantly in terms of characteristics: Patients with EA are mostly newborns or infants. When the newborn cannot swallow properly for a prolonged period of time, feeding difficulties persist even after esophageal reconstruction [4]. Early restoration of the esophagus seems therefore important. In contrast patients with extensive esophageal strictures due to caustic injuries or reflux esophagitis are usually much older and have swallowed properly before.

Jejunum as esophageal replacement has the advantage that its size matches the esophagus relatively well. Moreover jejunum either as a pedicle graft or as a free revascularized graft retains its peristaltic activity [2, 3, 5–8]. I got interested in jejunal pedicle graft reconstruction of the esophagus after visiting Mario Kasai in Sendai in 1981. Kasai had been using jejunal pedicle grafts for esophageal carcinoma and for caustic stricture [9], a technique he learned from his predecessor [10]. I used the technique for the first time in 1988 as a primary procedure in a child with pure esophageal atresia [1]. Altogether I have been involved in 28 jejunal reconstructions of the esophagus in children. This chapter is based on this personal experience.

Surgical Technique and Operative Steps [1–3]

The Preoperative Period

Most children requiring esophageal replacement will have received a gastrostomy earlier on. Preferably it should be created in the left hypochondrium via an upper midline incision, because this scar can be incorporated in the laparotomy incision for the definitive operation.

In children with a pure EA, a proximal fistula should be actively looked for. The incidence of a proximal fistula in the absence of a distal fistula is relatively high [11]. If such a proximal fistula is diagnosed, then the definitive procedure should not be delayed. A cervical esophagostomy should be avoided for two main reasons: firstly, the dissection interferes with the nerve supply of the

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proximal pouch, which is likely to cause additional problems [12], and, secondly, it results in a longer gap to be bridged. If an esophagostomy cannot be avoided, this should be done on the right side, avoiding the region of the aortic arch, as the interposition will also be done on the right as well. If the aortic arch descends on the right, then the procedures should be performed on the left, but this did not happen in the present series.

Before embarking on a jejunal interposition procedure, it is wise to exclude an intestinal malrotation, which has a higher incidence in children with EA [13, 14]. In the event of a malrotation, the vascular supply of the jejunum may preclude its use as happened in one of the patients not included in this series. In this patient with pure esophageal atresia, a gastric pull-up was performed. In a patient with EA and a distal fistula but very short upper esophagus and two failed attempts of a primary anastomosis, a pedicle ileal graft was used for bridging the gap [15]. This patient is also not included in this series.

The day before surgery, the large bowel is washed out in order to have all surgical options for interpositions available. Cleanliness of the colon is checked on the operating table when the child has been anesthetized.

Taking Down of the Cervical Esophagostomy

If a cervical esophagostomy has been performed, this should be taken down first. The detachment of a right-sided esophagostomy can be done in the same lateral decubitus position of the patient, which is used for the right-sided thoracotomy. In case of a left-sided esophagostomy (but normally descending aorta), the patient needs to be repositioned for the right-sided thoracotomy. Care should be taken to avoid further loss of esophageal material. After detachment of the esophagostomy, the region behind the trachea is bluntly dissected down into the right superior mediastinum. The tip of the esophagostomy is "parked" there. The track between the cervical incision and right upper thorax can be dilated with Hegar dilators.

Thoracoscopic Approach

To be sure that an interposition is needed, nowadays, the right chest is always investigated by a thoracoscopy first. There is no need for a single lung ventilation. The child is placed in a true left lateral decubitus position at the left edge of the operating table. The table is tilted 15° to the left and 15° head up position. The right arm is positioned over the head of the patient so that the axilla is accessible. The surgeon stands on the left side with the cameraperson below him and the scrub nurse at the lower end of the table. The principal screen is in front of the surgeon on the upper right side of the table. First 6 mm cannula is introduced slightly distal and more anteriorly than the inferior tip of the scapula. A 5 mm 30° telescope is used. After being sure that the telescope is in the pleural cavity, CO_2 is insufflated at a pressure of 5–8 mmHg and a flow of 0.1–0.5 L/min.

In cases with EA/TEF, the dilated upper pouch with thickened wall is easily seen. Usually the upper pouch reaches up to the azygos vein. The body of the esophagus may be absent, but a small esophageal remnant is usually present at least above the diaphragm. In between both ends of the esophagus, the vagal nerves are clearly visible. Identification of the lower esophagus is much simpler thoracoscopically than open. Both ends of the esophagus can be mobilized. For doing so, two more cannulas, but now 3.5 mm in diameter for 3 mm instruments, are inserted, one more proximally and one more distally in the midaxillary line. If the patient has a proximal fistula, this fistula can be dealt with thoracoscopically. Just the ends of the upper and lower esophagus are mobilized as extensive mobilization interferes with circulation and innervation. If it has been decided to remove the distal esophagus, much of this dissection can be done thoracoscopically.

When the esophagus is strictured either due to reflux or caustic injuries, the involved segment can be dissected and removed thoracoscopically. Since the patient will need a thoracotomy later on anyway, not much time should be lost though in doing this thoracoscopically.

Thoracotomy

Since a jejunal interposition requires fashioning of one anastomosis high in the chest and a second one low in the chest, a wide exposure is mandatory. A classic posterolateral thoracotomy is performed sparing the serratus anterior muscle. The chest is entered through the bed of the sixth or seventh rib after complete subperiosteal removal of the rib from its head all the way to the chondro-osseous transition. It is important to incise the anterior as well as the posterior periosteum right in the middle along its longitudinal axis. When these incisions are separately closed with fine sutures at the end of the procedure, the rib will regenerate nicely. The azygos vein is transected. For the identification of the proximal pouch, the anesthesiologist is asked to push on the Replogle tube which sits in the proximal pouch. The distal pouch is situated very posteriorly and can be traced by looking at the vagal nerves. The overlying mediastinal pleura is opened. There is no need to mobilize the pouches extensively as the gap will be bridged with jejunum. If the proximal pouch is to be mobilized, it should be done laterally and posteriorly. There is no need to separate it from the trachea. The coexistence of a proximal fistula should have been excluded preoperatively. The vagal nerves should be saved but this may be impossible when these nerves are imbedded in a diseased esophageal wall. The distal esophagus may be mobilized extensively when removal is planned. After the initial thoracotomy, the chest is closed by skin suturing only. This is done with a running 3×0 nylon suture.

Abdominal Steps

Dissection of the Hiatal Region

The patient is put in a supine position. The gastrostomy catheter is removed and a midline incision made from the xiphoid process down to and around the left side of the umbilicus. It is amazing how much exposure is gained by going around the umbilicus. The gastrostomy is detached from the abdominal wall and provisionally closed.

A retractor is placed underneath the left lobe of the liver. The fundus is detached from the diaphragm, and the upper short gastric vessels are dissected, which gives access to the lesser sac and posterior hiatus. The left crus is freed, the posterior hiatus opened, and a large window made into the right chest. The passage from the abdomen into the right chest should allow easy passage of the transplant into the right chest. Dilatation of the passage with Hegar dilators is an option.

The Cardioesophageal Region

When the lowermost part of the esophagus has been destroyed, e.g., by reflux or caustic injury, it should be resected. As mentioned earlier, much of this dissection can be done thoracoscopically. In esophageal atresia without fistula, the most distal part of the esophagus is intact although it may contain tracheobronchial remnants with or without cartilage [16]. Moreover achalasia-like symptoms have been described in association with esophageal atresia [17]. But irrespective of the primary pathology, signs of functional obstruction occurred in all patients in which the distal esophagus was saved. It seems therefore better to resect the distal esophagus and to anastomose the jejunal transplant directly to the cardia. This does not seem to cause problems of jejunitis due to acid reflux, not even at long-term follow-up [5, 18]. In the present series, the distal esophagus was resected in one patient with esophageal atresia and in the two patients with peptic strictures. If resection of the distal esophagus is planned, the distal esophagus should be mobilized and brought into the abdomen at this stage of the operation.

Preparation of the Pedicle Graft

The creation of the pedicle graft is the most critical part of the operation. The first two or three mesenteric vessels are divided between ligatures close to the main mesenteric route (Fig. 31.1a, b). The mesenteric lymph nodes should be removed so that the vessels can be well inspected over their entire length. Tiny vessels can be coagulated with a monopolar diathermy tip. The proximal jejunum is transected close to the ligament of Treitz but leaving enough proximal jejunum for easy restoration of continuity later on. The blood supply to duodenum is not a problem, even not when the first mesenterial branch is taken. Transection of

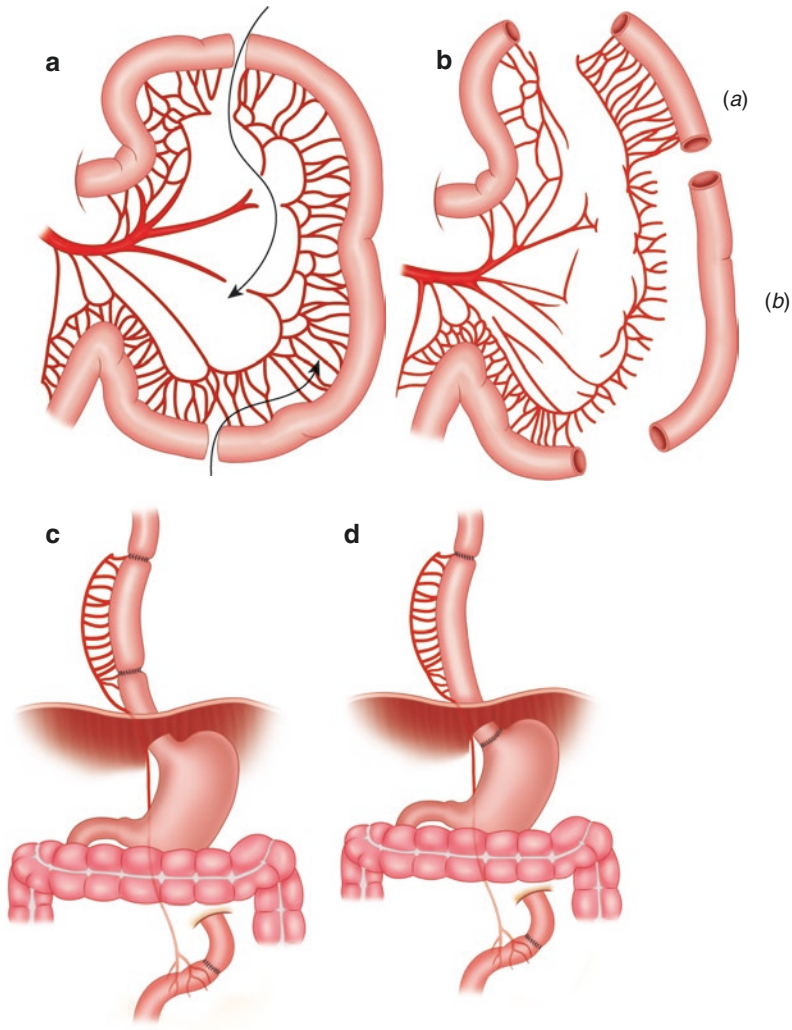

Fig. 31.1 (**a**–**c**) Schematic presentation of orthotopic jejunal pedicle graft reconstruction of the esophagus (Reprinted with permission, *Pediatr Surg Int* 1994 [1]). (**a**) The jejunum is transected close to Treitz ligament. The first two mesenteric arteries and venous branches are centrally divided between ligatures, leaving the peripheral arcades intact. The jejunum is transected again at the level of the third mesenteric artery and venous branch. The distal part of the upper jejunum is skeletonized close to the bowel wall. (**b**) The distal part of the jejunum (*b*) has been removed, leaving the uppermost part (*a*) for transfer into the chest. (**c**) The uppermost part of the jejunum has been transferred through the left mesocolon, behind the stomach, and through the posterior part of the hiatus into the right chest, were a double anastomosis has been made. Jejunal continuity in the abdomen has been restored behind the pedicle. (**d**) The distal esophagus has been resected. The uppermost part of the jejunum has been transferred through the left mesocolon, behind the stomach, and through the posterior part of the hiatus into the right chest. The graft has been anastomosed with the upper esophagus in the chest and with the cardia in the abdomen. Jejunal continuity in the abdomen has been restored behind the pedicle

the first two mesenterial branches has usually sufficed to reach the proximal esophageal pouch. In one patient with very short upper esophagus and high cervical esophagostomy on the left, the third branch had to be taken as well. The mesentery of the jejunal loop is now inspected. It is sometimes possible to save central arcades thereby leaving the peripheral arcades intact. More length is gained by skeletonizing the first centimeter of the proximal part of the future graft. This is done between fine absorbable ligatures, which will remind the surgeon at all times that this is the proximal part of the graft. By laying the distal jejunum over the chest, an idea is obtained as to

whether the graft will reach the upper esophagus. The graft should reach the neck. The circulation of the jejunum is watched all the times. No gauzes should cover the jejunum as this traumatizes the graft and hampers observation, but regular moisturizing is important. The jejunum is severed again opposite the level of the third mesenteric branch. Only jejunum is taken, not the arcade. The isolated jejunum is far too long. Only the most proximal part will be used. In infants with true long gap esophageal atresia not more than may be 5 cm is needed. This means that the rest has to be removed. This is done starting at the distal end of the graft. The best way of doing this is to use a monopolar diathermy needle right onto the serosa of the bowel. This should be done with care and short bursts of diathermy to avoid more central coagulation. Alternatively fine bipolar diathermy can be used. The mesentery has two leaves which should be diathermized separately. Some burning of the serosa is unimportant as this part of the graft will be removed. The upper part of the jejunum serving for the interposition should not be too long. Further skeletonizing of the graft later on in the chest is difficult as overview is lacking. The last 2 cm of skeletonized distal jejunum will remain well vascularized. If the graft is too long, these last 2 cm can easily be removed later on. Before starting to remove the distal part of the graft, the graft often looks a bit dusky, but during the process of removal of the distal part of the graft, the circulation to the remaining graft improves considerably.

Bowel continuity is restored behind the pedicle of the graft. The left part of the gastrocolic ligament is opened and a hole is made in the left mesocolon, close to its posterior insertion. The graft is passed through it taking care that the pedicle does not twist. Next the graft is passed underneath the remaining short gastric vessels to reach the area between the fundus and the spleen. The graft is then passed through the posterior hiatus into the right chest, which should go easily. Care should be taken to pass the proximal part first. The position of the pedicle is checked over and over again. If the lower esophagus is resected, the distal part of the graft should remain in the abdomen. The abdominal skin incision is closed quickly with a 3×0 running nylon suture.

Continuation in the Chest

The time between putting the graft into the chest and reopening of the chest should be short as the graft may have become kinked during its transport. The patient is repositioned in a left lateral decubitus position and the chest reopened. The graft is identified and positioned. When the surgeon intends to use the distal esophagus in esophageal atresia without distal fistula, the distal esophagus should be opened longitudinally in its posterolateral area before any trimming of the graft. One should make sure that the distal part is widely patent. In one of our patients, the distal segment was stenotic over about 2 cm, which was only realized after the graft had been trimmed resulting in an anastomosis under tension and postoperative leak. There is no need to transect vagal branches unless they are part of the destructive process. Next the upper pouch is opened. This is done with the diathermy needle over the pushed up Replogle tube. By doing so, this esophagostomy will be right in the middle of the distal wall of the pouch. This esophagostomy is then extended with scissors upward posterolaterally on the right.

An anastomosis is made between the upper esophagus and the proximal end of the graft using interrupted 5×0 absorbable sutures. The distal end of the graft is then trimmed and an end to side anastomosis between the graft and the distal esophagus is then made (Fig. 31.1c). Alternatively the distal anastomosis is made in the abdomen after resection of the distal esophagus. Before finishing the anastomosis in the chest, a nasogastric tube is passed through the graft. A chest drain is inserted and the thoracotomy closed in layers. Much attention is paid to close the posterior and anterior rib bed separately with 5×0 absorbable sutures.

Final Continuation in the Abdomen

The patient is repositioned supine and the abdomen reopened. If the distal anastomosis has still to be made, the distal esophagus is resected, the graft trimmed when needed and anastomosed to the cardia with interrupted 5×0 absorbable sutures (Fig. 31.1d). No antireflux procedure is

added. The gastrostomy is refashioned and the abdomen is closed.

Postoperative Care

The patient is weaned from the ventilator when appropriate. It is important to keep the patient well hydrated as fluid will sequestrate into the chest and abdomen. Gastrostomy feedings are started when there are no gastric retentions anymore. The chest drain is removed after 5–6 days after a contrast study has ruled out any leaks. Oral feeding is then started. It is important to control the patient regularly on an outpatient basis to check for stenoses. In case of a distal stenosis, the graft will dilate, which is to be avoided at all times.

Results

In a period of slightly over 20 years (1988–2009), 28 orthotopic jejunal pedicle graft interpositions have been carried out. Adding the two patients that had another form of interposition all together, only 30 patients were treated with an esophageal substitute indicating the rarity of such procedure. Besides these 30 "in-house" patients, 11 were operated outside the author's home institution. To gain and to keep enough experience in this field of pediatric surgery, these patients should be centralized.

Indications		Age at interposition
Esophageal atresia	21	
Primary interposition	17	76 days median (range, 16–309)
No fistula	11	
Proximal fistula	6*^{R}	
Secondary interposition	4	50, 120, 1080, 1100 days
No fistula	2	
Distal fistula	2*^{L}	
Caustic stricture	4	1, 3, 5, 16 years
Peptic stricture	2	10, 14 years
Battery necrosis	1*^{R}	2 1/2 years
Total	28	

^{R}Right, ^{L}left
*Stands for the one cervical esophagstomy

Early Results

The results of the first 24 jejunal interpositions, 19 for esophageal atresia, 3 for caustic stricture, and 2 for peptic stricture, have been described in detail elsewhere [3]. The median follow-up at the time of that publication was 5.5 years in the esophageal atresia group, 4.4 years in the caustic stricture group, and 7.4 years in the peptic stricture group. Since that publication four additional jejunal interpositions were carried out.

None of the 28 grafts were lost, but postoperative respiratory distress syndrome occurred in three patients of the esophageal atresia group that had a primary interposition.

There were five early postoperative leaks in the esophageal atresia group, four in the chest and one in the abdomen. One leak in the chest and the only leak in the abdomen were treated surgically. In one patient a proximal fistula had been missed primarily and required ligation through the neck in a second operative session. One patient developed early distal graft anastomotic occlusion requiring surgical correction. Dilatation in this patient could not be performed as the nasogastric tube had been removed prematurely and no lumen could be seen at esophagoscopy. There were no leaks in the remaining patients except for one of the patients with an extensive peptic stricture. That patient had multiple previous operations. The leak settled by chest drainage. In one of the patients with caustic stricture, there was a postoperative intra-abdominal bleeding requiring re-exploration, but no major source was found. The same patient had a pyloroplasty later on because of ongoing gastric outlet obstruction.

Long-Term Results

One patient has died so far. He had trisomy 21 and esophageal atresia without fistula. He developed severe respiratory distress postoperatively. He was never able to eat and was always fed by gastrostomy. He was cared for in an institution and died suddenly. The exact cause of death is unknown.

Anastomotic dilatation was required in 12 patients, 10 of them belonging to the atresia

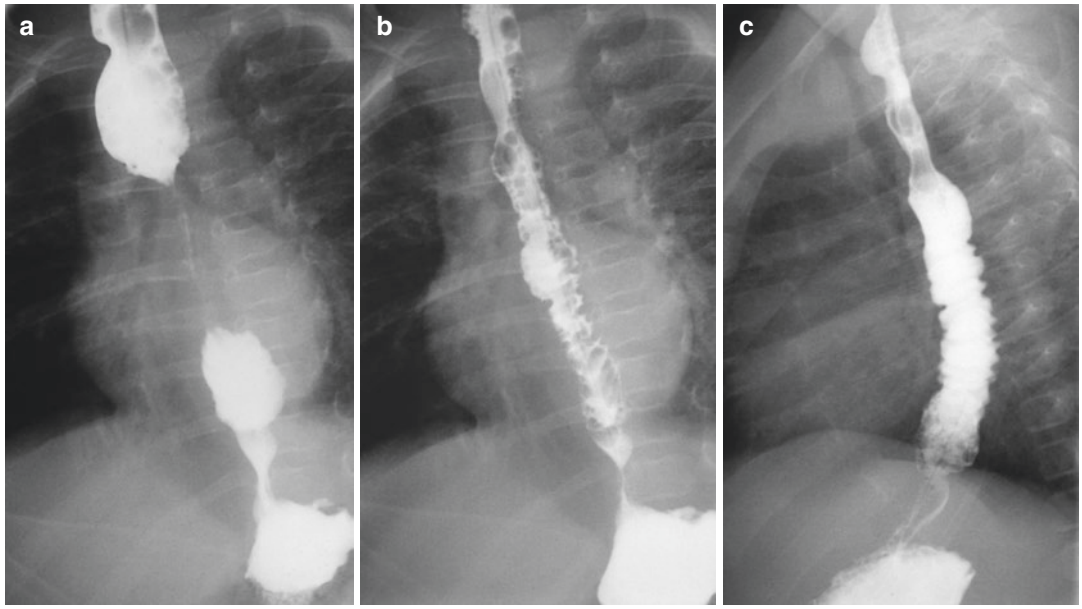

Fig. 31.2 Barium meal 3 months after jejunal grafting (Reprinted with permission *J Pediatr Surg* 2007 [3]). (**a**, **b**) Anteroposterior view showing vigorous contractions and emptying of the jejunal graft. (**c**) Lateral view

group. Six patients were dilated five times or more. In one patient the graft was perforated during dilatation requiring thoracotomy for closure.

With time there was no tendency for the graft to elongate, but there was always some obstruction at the distal anastomosis, which appeared functional in most of the patients. This led to widening of the graft in one of the patients. A widening plasty of the distal anastomosis was unsuccessful. Finally the distal esophagus was resected and the very much dilated conduit was anastomosed to the stomach. Significant reflux and pulmonary problems resulted.

Reflux in the other patients was not a problem even not in the patients with resected distal esophagus. On barium swallow there was always vigorous peristalsis of the graft (Figs. 31.2 and 31.3). Most patients are eating everything and bolus obstruction is rare. Most patients grow well.

Discussion

Especially in long gap esophageal atresia, pediatric surgeons have embraced the adagio "the child's own esophagus, no matter what has to be safely done to bring it together, is infinitely better than any replacement that can be constructed" [19–22]. That the healthy own esophagus is best is beyond doubt, but this does not necessarily apply to the diseased esophagus. In esophageal atresia without distal fistula, the esophagus is largely absent. It is not a matter only of getting the ends together, it is a matter of function. In order to unite the two ends of the esophagus, the remnants have to be mobilized extensively, which impairs esophageal function further. The risk of stricture and severe gastroesophageal reflux after primary repair is as high as 30 % [21]. Moreover reflux in these patients is very difficult to treat. Looking from the medical point of view, the long-term results after esophageal atresia repair are not very good, which contrasts with quality of life assessments [12–15, 23–26]. This conflict is undoubtedly caused by the fact that the patient doesn't know better.

The question of course arises whether an esophageal replacement in these patients would be better. Maish and DeMeester wrote that any replacement suffers from a lack of effective peristalsis and the absence of a physiologic barrier to reflux [27]. This statement does not hold fully true regarding the jejunum. A jejunal graft does not display a normal motility, but retains peristaltic activ-

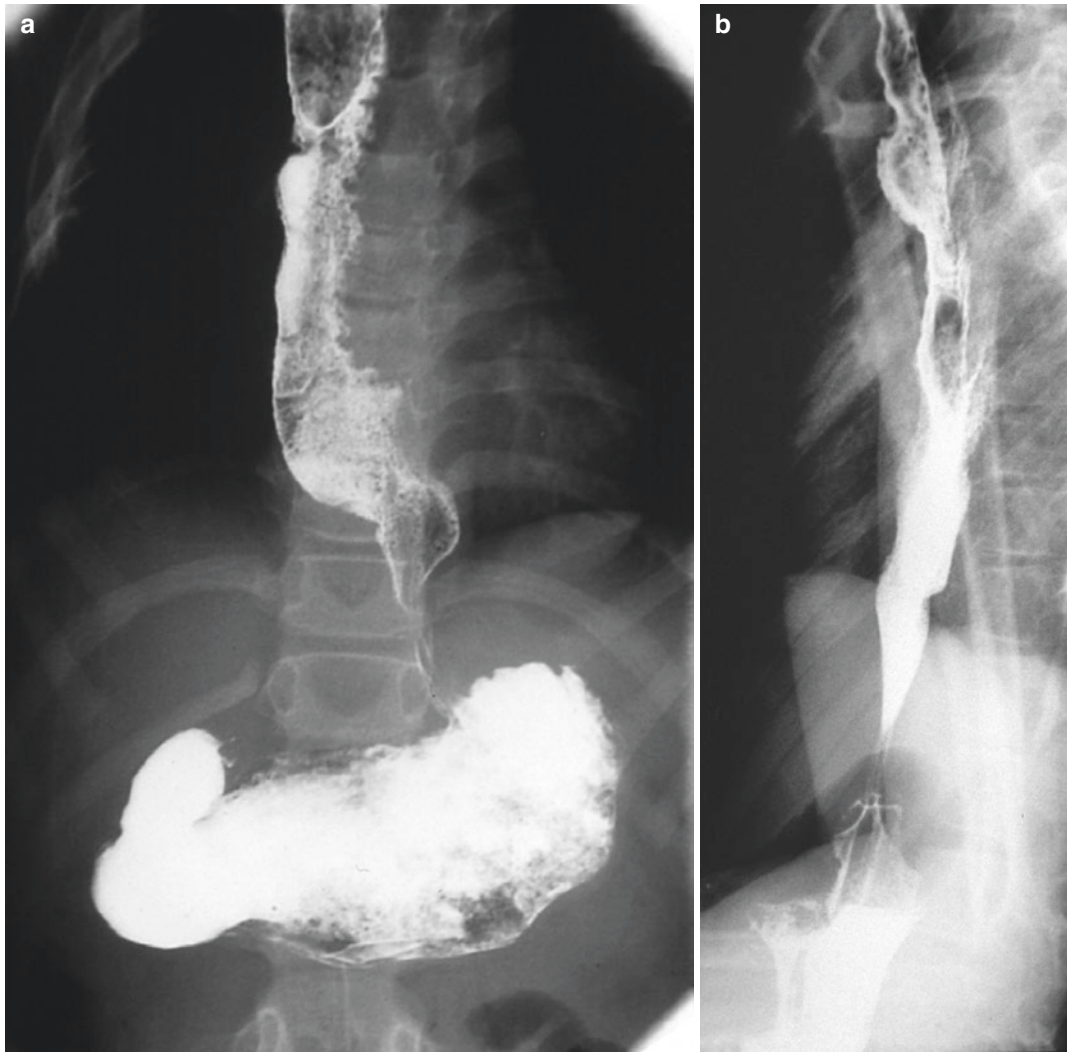

Fig. 31.3 Barium meal in another patient, 7 years after grafting [3] 3 months after jejunal grafting (Reprinted with permission *J Pediatr Surg* 2007 [3]). (**a**) Anteroposterior view. (**b**) Lateral view

ity [1–3, 5–8, 28, 29]. Contractions are rather segmental than peristaltic, which accounts for a delayed transit time [29]. Interestingly, none of the adult patients described by Wright et al. admitted to dysphagia for liquids or solids on direct questioning [29]. In adults free jejunal grafts showed phase III migrating motor complexes, which were not interrupted by swallowing water [8]. But again, swallowing in the vast majority of adult patients with a free graft in the neck is good [6, 7]. Swallowing function was also good in the 10-year-old child who had a free jejunal graft [30].

In contrast as what would be expected, jejunum when used as a distal esophageal substitute seems to act as barrier against reflux [5, 18, 29]. Recently, replacement of the distal esophagus with jejunum in adults as a treatment of early adenocarcinoma is gaining more attention [31]. Reflux in these patients does not seem to be a problem.

In pediatric surgery jejunum as an esophageal substitute has never gained real acceptance. A few relatively large series of pedicle grafts however have been reported. Ring et al. published in 1982 a series of 32 children with 18–33-year follow-up in

16 of them [32]. They used a staged approach. In the first procedure, the graft was placed antesternally but was moved subsequently into a retrosternal position through a sternotomy. All grafts reached the neck and none of the grafts was lost. All patients could eat a regular diet. A second large series was published by Saeki et al. in 1988 [33]. The technique used was very much the same as the technique presented in this chapter, except for doing two right-sided thoracotomies, one through the third and one through the seventh intercostal space and except for the relative late timing of the reconstruction. Only one graft was lost. Cusick et al. [34] used jejunum in six esophageal atresia patients, but two of the six patients died. The graft was put in a retrosternal position, and five of the grafts received a dual blood supply by anastomosing the terminal arcade vessels to vessels in the neck. In the last patient, a free graft was used with success. In most studies in children regarding jejunal pedicle graft interposition, the distal part of the graft was anastomosed directly to the stomach [32, 34]. One of the reasons for not using the distal esophageal remnant has been the observation that the distal esophageal remnant may contain abnormal embryonic tissues such as cartilage [35, 36]. I originally thought that the distal esophagus should be retained whenever possible in order to prevent reflux. In all patients in whom the distal esophagus remained in place, however, some hold up of contrast was seen in the distal part of the jejunal interposition and the retained esophagus did not open up nicely. A number of patients were dilated for that reason. In one patient the functional obstruction resulted in marked dilatation of the graft. Eventually we had to resect the distal esophagus, but this created a common channel of dilated jejunum and stomach with reflux and respiratory symptoms. In the patients with peptic stricture of the esophagus and in one patient with esophageal atresia, the distal esophagus was resected and a direct anastomosis with the upper stomach was performed. In these patients there was no distal functional obstruction. Moreover reflux has not been a problem, which is in line with observations in adults [5, 18, 29].

Gaining enough jejunal length has not been a problem. In all but one patient of this series, however, we replaced the middle part of the esophagus in the esophageal atresia and caustic burn patients and the distal esophagus in the patients with peptic stricture. If the more proximal esophagus has to be replaced, getting enough jejunal length may be a problem. In one patient the jejunum was brought up into the neck, which resulted in a tortuous graft. When a high replacement of the esophagus is required, an ileal pedicle graft may be better [15].

Age at which replacement of the esophagus is required is not a contraindication for jejunal interposition. If a patient with esophageal atresia without distal fistula tolerates suctioning of the upper pouch well, the interposition can be postponed until the end of the neonatal period. If, however, problems of recurrent aspiration occur, the time of the interposition can be advanced. Under such circumstances one should reconsider the presence of a proximal fistula. If such a fistula is present, it can be dealt with at the time of the interposition, either through the neck or thoracoscopically. It is important not to defer the reconstruction for too long. Swallowing seems not a problem in esophageal atresia without fistula when the reconstruction is carried out before 6 months of age.

One should try to avoid the creation of a cervical esophagostomy but if this is not possible, it should be created on the right side as the interposition will be done through the right chest. By choosing for the right chest, the aortic arch is not in the way as long as it is descending normally. If the esophagostomy is on the left, it can be mobilized and tunneled behind the trachea into the right chest. But this maneuver is more difficult than if the esophagostomy was on the right. Moreover it requires repositioning of the patient for the thoracoscopy/thoracotomy.

As said before, intestinal malrotation should be excluded before embarking on jejunal pedicle graft reconstruction of the esophagus.

Esophageal replacement with jejunum in children is a demanding operation with considerable morbidity, but in this series there was only one late mortality and none of the grafts were lost. Moreover long-term function in most patients was good. Jejunal pedicle grafting should be part of the armamentarium of pediatric surgeons dealing with complex esophageal reconstruction.

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32 Oesophagus Tissue Engineering: Future Options in Oesophageal Replacement Through Regenerative Medicine

Amulya K. Saxena

Introduction

Despite the notable success of oesophageal replacement procedures, such as gastric, small intestine and colon transposition and gastric tube formation, these techniques are associated with a high incidences of complications including leakage, stricture, elongation and malnutrition due to shortening of the gastrointestinal tract and are the main reasons driving research in oesophagus tissue engineering [1–3]. Recent studies exploring the use of biomaterials for oesophageal replacement have also been hindered by severe limitations including slow ingrowth of cells onto the biomaterial grafts from surrounding tissue and little to no muscle regeneration [4]. Consequently, there is an urgent requirement for viable alternatives which bypass such complications, and the emerging technology of tissue engineering may provide much needed solutions.

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Tissue Engineering and Regenerative Medicine

Tissue engineering began as a branch of biomaterial science, in which scientists involved in polymer chemistry investigated the interaction of cells with newly developed biodegradable materials. The enormous potential of this unique area of research soon became aware and was reflected by a European public expenditure of €10 billion in the period between 1994 and 1998 [5]. The rapid emergence of regenerative science in medicine led to the establishment of *tissue engineering* as a field in its own right within the area of biotechnology.

Tissue engineering is a multidisciplinary science applying the principles of engineering to the fields of clinical medicine and cell biology. The complexity of this field of research requires contributions of experts from various specialties and the accumulation of knowledge from interrelated disciplines, for progress to be achieved. The multidisciplinary approach of tissue engineering begins with the identification of pathologies that require tissue engineering solutions based on clinical experience and epidemiological data. Basic science is then referred to in order to better understand the structure and physiology of tissue and organs so that the blueprints of the organs to be engineered may be drawn. The options of various sources of cells for tissue engineering are

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explored, and scaffold materials which act as carriers for cell attachment and organisation are designed and fabricated from natural or synthetic materials in line with requirements of the target organ. Growth factors and such biomolecules may be attached to the scaffold surfaces to promote biosignalling and influence attachment, proliferation, differentiation and organisation of cells [6]. As the unique demands of in vitro culture are realised, techniques for the proliferation of large quantities of cells and the design of scaffold architecture to allow for the seeding of cells within the core of scaffolds must be investigated [7]. In order to keep cells viable for prolonged periods of in vitro cell culture, devices have been designed such as the flow bioreactor which may enhance cell seeding and improves mass transfer of nutrients and gases. Similarly, alternative in vivo strategies have been developed by surgeons in which the body is utilised as an in situ bioreactor. Throughout the phases of tissue engineering research, contributions from diagnostics, imaging and other biomedical fields are continuously applied to assess the success of tissue-engineered constructs and provide feedback to the cell biologist and polymer scientists.

The Concept of Tissue Engineering

The concept of tissue engineering has its origins in experiments of the 1930s in which organs were cultured ex vivo with the aim of repairing or replacing damaged or diseased organs [8]. It was only in the late 1980s that scientists, engineers and clinicians began to study the possibility of de novo tissue generation as a solution to the acute shortage of organs for transplant. The basic concept of tissue engineering is similar, irrespective of the tissue or organ to be engineered. Cells are sourced, isolated and proliferated. Scaffolds are fabricated and seeded with cells to create a construct which is cultured within an in vitro or in vivo bioreactor. The specific issues related to this technology including cell sourcing, scaffold selection and systems of cell culture will be addressed in the following subsections.

Cell Source

The engineering of neotissues requires a suitable source of cells. The criteria of an appropriate cell source for tissue engineering are as follows. The cells should be easily obtained, be capable of substantial expansion in number in vitro, survive implantation, avoid immune rejection, display normal function and must not show malignancy. Cells may be procured from the patient's own cells (autologous), which are immune compatible, or from human donors (allogenic), which offer off-the-shelf availability yet have issues with immunocompatibility and theoretical risk of infection. After the appropriate cell source has been selected, functional characteristics of the cell may be manipulated via stimuli from the microenvironment or genetic manipulation. Genetic manipulation could be used to programme the cell for specific tissue engineering purposes including the inhibition of immune responses, alteration of matrix synthesis, improvement of cell proliferation and the enhancement in secretion of specific biologically active molecules. For tissue engineering of the oesophagus, a wide variety of cell types are required. Principally, the two major cell types are epithelial and muscular cells. In addition the tissue-engineered oesophagus required endothelial cells for vascularisation and neurogenic cells for innervations as well as connective tissue for maintenance of structural integrity. Cell sources generally can be categorised as mature or progenitor cells, the latter of which is best represented by the adult stem cell. The pros and cons of both groups are detailed below.

(a) *Mature cells*
Mature cells are fully differentiated cells of a specific cell type. Such cell types can be obtained through a biopsy and expanded in number in vitro to produce the desired cell number for tissue engineering. Mature cells are traditionally isolated from tissue via the "explant" culture technique whereby a small biopsy of tissue is glued to the base of a tissue culture plate [9] (Fig. 32.1). Over a period of culture, cells grow out from the

biopsy and invade the tissue culture plastic. These cells have the benefit of not requiring any in vitro manipulation to produce the desired phenotype. The major drawback is the relatively poor proliferative capacity of mature cells. Whilst the explants technique produces sufficient success in particular cell types, other cell types show a slow rate of outgrowth and are prone to becoming overrun by fibroblast contamination. In response to these limitations, alternative techniques for optimising cell isolation and improving cell proliferation have been researched and will be discussed in section "Tissue Engineering of the Oesophagus" [10].

(b) *Adult stem cells*

Precursor or progenitor cells have the principle benefit of a high proliferative capability. In recent times there has been a great interest in the application of stem cells for tissue engineering, with the focus of attention on embryonic (ES) and adult stem (AS) cells. ES cells are sourced from discarded human embryos. These cells show a high degree of plasticity; however, generation of pure populations of desired cells is problematic [11–15]. ES cells also have been associated with the risk of teratoma formation as well as ethical controversy over the use of embryonic tissue [16].

In comparison with ES cells and the associated controversies, adult stem cells present a more direct route to clinical translation. Whilst the capability of differentiation may be lesser than ES cells, AS cells also display potential for differentiation along a variety of lineages. Mesenchymal stem cells (MSCs) are a class of AS which have shown enormous potential in tissue engineering and regenerative medicine. MSCs give rise to cells of the mesenchymal lineage (bone, cartilage, tendon, muscle and fat) and have been much researched for applications in both musculoskeletal and vascular tissue engineering [17–19]. There is also evidence that MSCs have a capacity for differentiation into cell types outside of the mesenchymal lineage. Others demonstrated that MSCs cultured on an air-liquid interface displayed phenotypes similar to those of airway epithelial cells.

Initially, MSCs were identified in the bone marrow, in which they exist in relatively high concentrations [20, 21]. Since then, MSCs have been further identified in a wide range of tissues including adipose tissue which can be easily obtained through liposuction procedures [22].

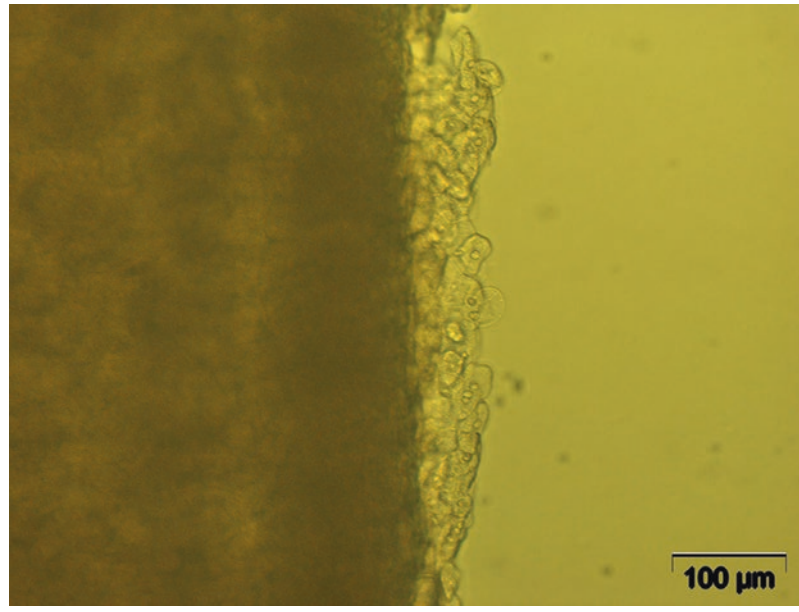

Fig. 32.1 Rodent oesophageal epithelial cell isolation using the explant technique showing the light microscope image early phase of cell detachment from the explants in vitro

MSCs can also be sourced from amniotic fluid or chorionic villi and can give rise to cell types representing all three embryonic germ layers [23, 24]. Amniotic fluid stem cells in particular can be proliferated over 200 times without senescence or telomere shortening. As with ES cells, safety concerns have also been raised with AS cells. By removing MSCs from their native environment and encouraging high levels of proliferation, there is an increased risk of tumorigenesis as observed by the development of sarcomas after implantation into mice of MSCs seeded onto bioscaffolds [25].

Scaffolds and Polymers

Scaffolds are supportive biomaterials which provide cells with an artificial extracellular matrix (ECM) allowing for the in vitro promotion of organisation towards tissue formation [26]. Ideally, a scaffold for tissue engineering should (a) promote cell-scaffold interaction, cell adhesion and deposition of ECM; (b) support cell proliferation, differentiation and viability through permitting the transport of gases, nutrients and metabolites; (c) display controlled degradation with non-toxic breakdown products; and (d) minimise the elicitation of inflammatory responses in vivo.

Biodegradable scaffolds can be produced from synthetic polymers such as poly(l-lactic acid) (PLLA), poly(glycolic acid) (PLGA), poly(ε-caprolactone) and polydioxanone (PDS) or biological biomaterials such as collagen, fibrin, alginates or chistosan [27]. Scaffolds can be designed and fabricated to produce a variety of architectures with regard to both the dimensions of the struts and fibres and the structure of the porous space within the scaffold. The structure and composition of a scaffold influence a range of factors including biomechanical function, biodegradation, cellular function and orientation of tissue. Scaffold architecture can be controlled by a variety of fabrication techniques including fibre bonding, electrospinning, extrusion, foaming, rapid prototyping and peptide self-assembly.

Scaffold matrices can also be derived from the decellularisation of tissues. Decellularisation enables the removal of cells whilst retaining the structure and function of the ECM. The ECM provides a multitude of functions from signalling to structural support. The presence of growth factors sequestered within decellularised tissue provides a bioactive element to these scaffold materials. Decellularised tissues such as small intestinal submucosa, porcine dermis and bovine pericardium have been used widely in reconstructive surgery and more recently in tissue engineering. Our group has also successfully decellularised the oesophagus and investigated it as a scaffold for possible tissue engineering applications [28].

In addition to solid-state scaffolds, there is an increasing application in tissue engineering of hydrogels fabricated from both synthetic and natural-derived materials [29–31]. Common, naturally derived materials for hydrogel fabrication include collagen, fibrin, hyaluronic acid, chitosan, alginates or silk fibrils, whereas synthetic hydrogels are commonly fabricated from polymers such as poly(ethylene glycol) (PEG), poly(vinyl alcohol) and poly(2-hydroxyethyl methacrylate).

Hybrid Constructs and Coculture

The engineering of complex organs requires the combination of multiple tissue types into a single construct. Such constructs may be realised through the hybrid construct or coculture approach (Fig. 32.2). Critically, in vitro, the optimal physiological culture conditions vary between cell types, with different cell types requiring specific media compositions and environmental cues. In the hybrid construct approach, homogenous cell types seeded onto scaffold sheets are first cultured in separation under cell type-specific culture conditions, followed by assembly of multilayered constructs of different cell types, prior to implantation in vivo [32].

In contrast, coculture involves first combining two or more cell components together onto

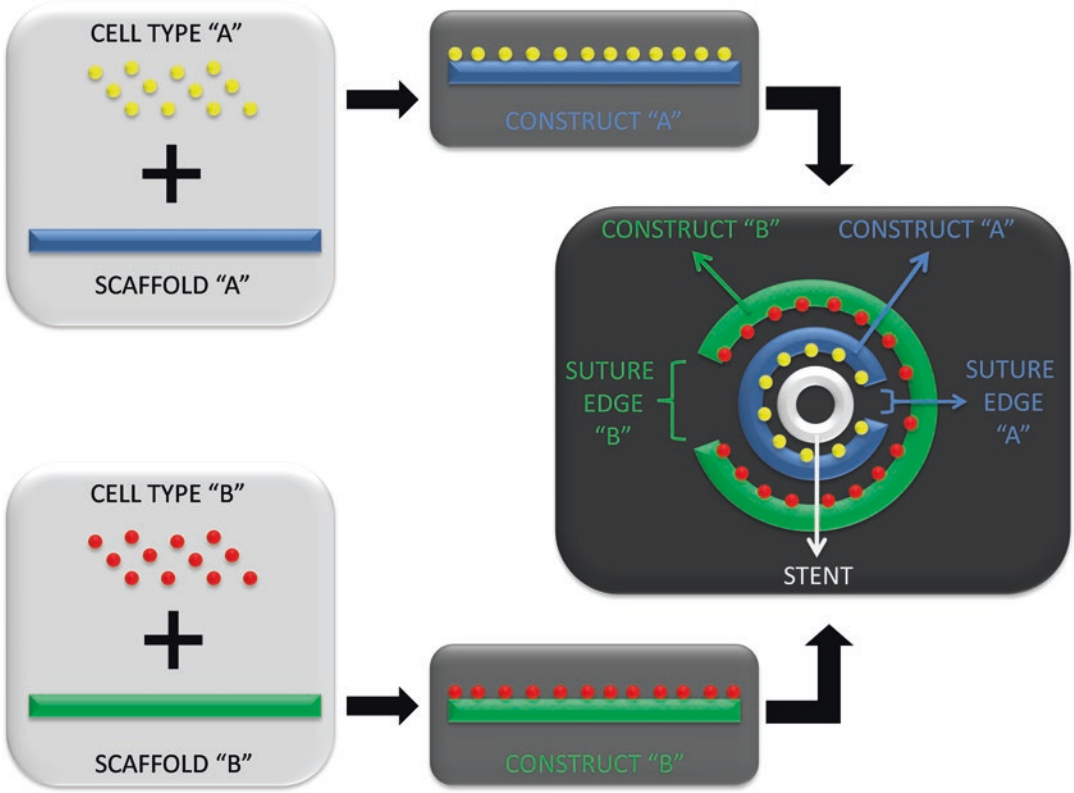

Fig. 32.2 Schematic representation of the concept of hybrid constructs formation for complex tubular organ tissue engineering

a single scaffold, followed by culturing in an environment whereby the requirements of the different cell types are provided for. Such a coculture approach often requires (1) the design of dual-layered scaffolds for the separation and organisation of the different cell types and (2) a device for isolating the different media types. An example of coculture can be seen in the tissue engineering of oral mucosa whereby one side of a scaffold was seeded with fibroblasts, whilst the alternate side was seeded with keratinocytes [33]. The construct was then cultured at an air-liquid interface in which the scaffold side seeded with fibroblasts was submerged in culture media, whilst the keratinocyte seeded surface was exposed to the air. The air-liquid interface encouraged organisation of a stratified epithelium whilst maintaining the viability of the underlying fibroblastic feeder layer.

Bioreactors

A bioreactor is a device for culturing of tissue-engineered tissues, providing a controlled environment with physical stimuli similar to those of the human body [34]. During traditional static cell culture conditions, cell-seeded scaffolds are maintained in a stagnant culture media in which media is changed at intervals of 24–48 h. The limitation of such systems is a continuous depletion of nutrients and gases accompanied by an accumulation of waste products. In comparison, the bioreactor offers dynamic cell culture conditions, whereby a pump system provides a constant and regulated flow of fresh culture media to the cells within the scaffold. Bioreactors, therefore, hold numerous advantages over traditional static culture techniques. The two major advantages are improvement in the efficiency of mass transport

of gases nutrients and regulatory factors and the provision of mechanical stimulation.

Bioreactor design has enabled the transmission of a variety of different mechanical stimuli to the cell/scaffold constructs including pulsatile flow, stretching, torsion and compression [35–37]. Such mechanical stimulation may improve proliferation, induce differentiation and promote the organisation of tissues [38, 39].

Perfusion bioreactors are also capable of seeding cells onto a scaffold, whereby they have control over the initial cell distribution within 3D scaffolds. A variety of commercial bioreactors are available to the tissue engineer. Based on the improved understanding of physiological conditions required for directing cell differentiation and tissue assembly, much progress has been made in the design of advanced bioreactors.

Tissue Engineering of the Oesophagus

There are many challenges in the engineering of the oesophagus. This begins with the anatomical complexity of this tubular organ. The oesophagus transverses three anatomical planes and varies according to localisation in both function and histological appearance [32]. Early studies investigating the possibility of cell-free biomaterials to replace segments of the oesophagus varied in success depending on the location of the oesophageal defect. For example, a double-layered tube of collagen sponge matrices on a silicon stent was utilised to replace a 5-cm cervical oesophagus defect in a canine model [40]. After removal of the stent at 4 weeks, oesophageal tissue was detected in the implanted scaffolds, and the animals were able to tolerate feeding. The same scaffolds applied to the repair of a 5-cm thoracic defect showed full regeneration of the mucosa within 3 months and of the glands within 12 months; however, formation of the muscularis mucosae was weak, with only islets of smooth muscle present after 12 months, whilst the skeletal muscle failed to extend towards the middle of the regenerating oesophagus after 24 months [41]. The poor regeneration of muscle layers was attributed to the lack of blood supply from surrounding tissues within the thoracic segment, although attempts to increase vascular ingrowth into the collagen scaffolds, via an omental wrap or basic fibroblast growth factor, also failed to improve the outcome [41, 42]. In addition to collagen scaffolds, decellularised scaffolds, including porcine small intestine submucosa and urinary bladder submucosa, have also been employed as oesophageal replacements in large animal models. These scaffolds showed migration of host tissue and coverage by skeletal muscle, yet suffered from strictures resulting in severe morbidity [43–45].

Other than highlighting the anatomical complexity of the oesophagus and its influence on regeneration, these studies also demonstrate how biomaterials implanted alone, without prior combination with a cellular component, result in delay and, in some cases failure, of tissue regeneration. To advance the rate of regeneration and to improve the overall outcome of such studies, recent research has adopted the tissue engineering approach for the repair of oesophageal defects. In principle, a tissue-engineered construct should mimic the structure and biomechanical properties of native oesophageal tissue, possess a luminal surface covered by a continuous epithelial layer and an orientated muscle component capable of contraction and must be readily innervated and vascularised, resulting in a functional and viable organ.

Tissue engineering of complex organs necessitates either a hybrid approach, which involved the generation of individual tissue grafts before assembly as a complete organ or a coculture approach whereby the different tissue components are cultured together. Initial experiments with the hybrid approach have led to the generation of oesophageal epithelium as well as the smooth muscle components in vitro [32]. Such studies form the basis for future in vivo implantation studies. Rat oesophageal epithelial cells (REECs) were isolated by a modified explant technique. Oesophageal epithelium was first mechanically separated from the connective tissue of the underlying mucosa and cut into 2–3 mm pieces. The oesophageal pieces were

attached to the surface of tissue culture dishes using a basement membrane matrix. Explants were then submerged in a specific media for the culture of epithelial cells. Explants were incubated at 37 °C and 5 % CO_2 for 48 h after which cells became dissociated from the epithelium and could be mechanically separated by a 10-mL pipette. After passing the cell solution through a 50-μm filter, cells were collected, resuspended onto tissue culture dishes and maintained in culture until confluence was reached (Fig. 32.3).

In the meantime, rat smooth muscle cells (RSMC) were isolated from the aorta. The tunica media was cut into pieces and glued to the base of tissue culture dishes using basement membrane matrix, before submerging in Dulbecco's modified essential medium (DMEM) and foetal calf serum. Explants were cultured at 37 °C with 10 % CO_2. After 7 days, RSMCs had begun to grow out from the explants. The explant tissue was removed, and adhered RSMCs were allowed to grow to confluence (Fig. 32.4).

The above-described explant technique for tissue isolation was found to be adequate for RSMC isolation; however, REECs cultured from mucosa explants were prone to becoming overrun by fibroblast contamination. The key obstacles to the engineering of an epithelial layer were, therefore, the efficient isolation of REECs from the original biopsy tissue and improvement of in vitro proliferation of REECs. In response, alternative techniques have been developed for the isolation of RECCs.

It was demonstrated that through enzymatic separation of the epithelial sheet from the underlying mucosa, fibroblast contamination could be minimised. Furthermore, mechanical disruption of the epithelial sheet resulted in the isolation of high cell densities [32]. The relatively poor proliferative capacity of EECs was addressed through the selection of specific subpopulations of EECs which display significantly higher rates of proliferation. In the large animal model (ovine), characterisation of various phenotypical subpopulations of ovine oesophageal epithelial cells (OEECs) demonstrated that 50 % of OEECs isolated from ovine oesophagi were proliferative [46]. Further investigation demonstrated the existence of a subpopulation of OEECs expressing markers for pan-cytokeratin 26 (PCK-26), which contained a percentage of proliferating cells significantly higher than that of the total population (Fig. 32.5). By isolating PCK-26+ cells through fluorescence-activated cell sorting and seeding onto collagen scaffolds, it was demonstrated that such high proliferating

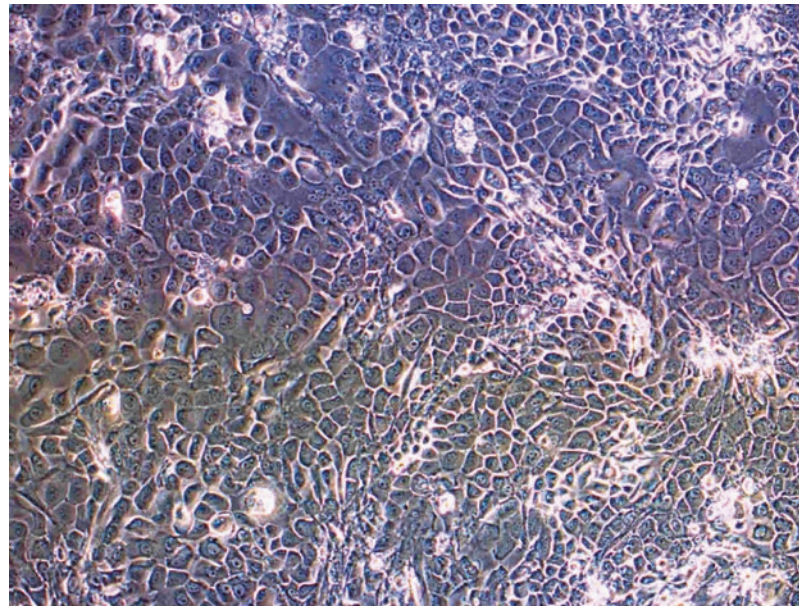

Fig. 32.3 Rodent oesophageal epithelial cells isolated using the explant technique reach confluence and differentiate to form sheets of epithelium on coated tissue culture dishes

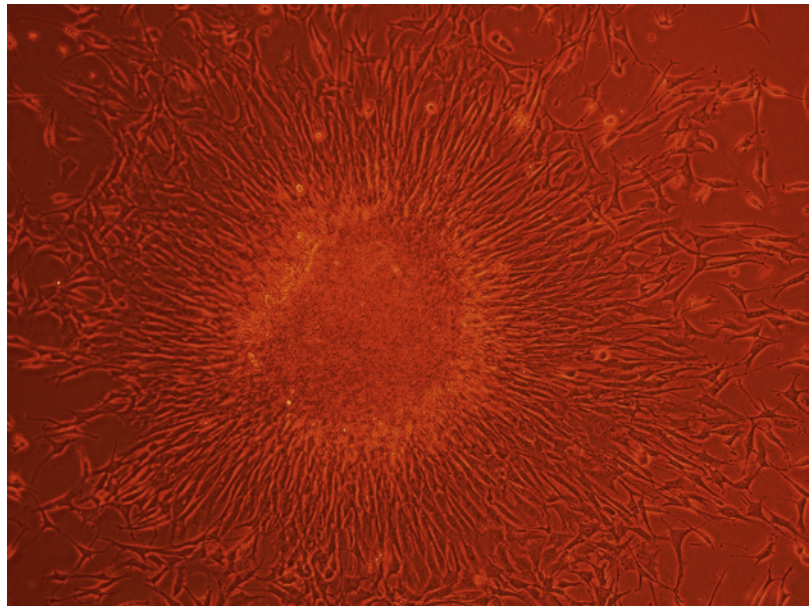

Fig. 32.4 Isolation and proliferation of smooth muscle cells from explants. Image shows the outgrowth of cell after removal of the explant and the first passage

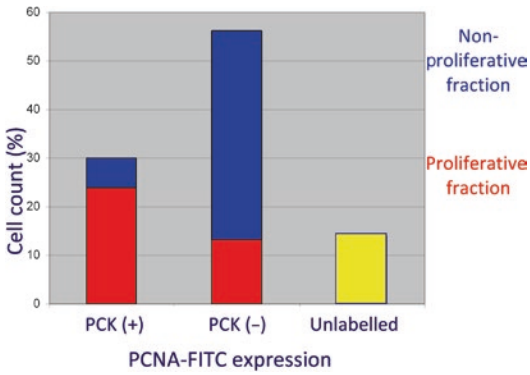

Fig. 32.5 Ovine oesophageal epithelial cells (OEEC) characterised by pan-cytokeratin markers (PCK-26) demonstrate that approximately 30 % of the OEECs are PCK-26+ and this subset has high proliferative capability that is necessary for generation of oesophageal epithelium

subpopulations produced a more uniform distribution of cells with a high attachment rate in comparison to unsorted cells.

Once isolated and cultured to suitable cell numbers, epithelial and muscle cells may be seeded on to scaffold materials. A scaffold, for tissue engineering of the epithelium, should encourage cell attachment and proliferation, and critically it should permit the organisation of a stratified epithelial layer. REECs were seeded onto both synthetic (PLLA, PLGA and PCL/PLLA) and natural scaffolds (AlloDerm®) to observe cell interaction [47]. After 18 days of in vitro culture, REECs seeded onto AlloDerm® showed a proliferative basal layer, epithelial stratification and a keratinised layer. In contrast, REECs seeded onto the synthetic scaffolds, with their highly porous structure, were unable to form a continuous epithelial layer.

The requirement of a smooth, 2D surface for epithelial layer formation has been further demonstrated in the comparison of EEC seeded onto 2D and 3D collagen scaffolds [10]. REECs seeded onto 3D collagen scaffolds failed to show organisation into an epithelium, whilst REECs seeded onto 2D collagen scaffolds formed a single-layer epithelial sheet after 3 weeks of in vitro culture.

In the generation of smooth muscle tissue intended for tubular tissues, it is important that the scaffold aids orientation of the muscle tissue to maintain proper structure and to generate coordinated muscle contractions in the tissue-engineered oesophagus. RSMCs isolated from the aorta were seeded onto collagen scaffolds containing either non-organised or unidirectional polymer fibres [32]. Constructs were assessed at regular periods by immunohistochemical techniques up until

8 weeks post cell seeding. RSMCs were shown to retain their phenotype during prolonged periods of in vitro culture, with markers for α-smooth muscle actin still detectable after 8 weeks. Furthermore, RSMCs seeded onto non-organised collagen generated non-organised smooth muscle tissue, whilst smooth muscle cells seeded on to unidirectional collagen polymers generated orientated smooth muscle strands. Such orientation of myoarchitecture can be used to mimic the circular and longitudinal configurations of the native oesophagus.

These studies demonstrate the importance of the scaffold in tissue engineering. By providing feedback to the biomaterial scientists, novel materials are being developed, designed to overcome particular obstacles. For example, to promote cell attachment and proliferation of OEECs, an electrospun scaffold was fabricated with a nano-topography [48]. The creation of nanopores within the fibres increased protein adsorption by 80 % and increased surface area by 62 %, resulting in the adherence of significantly greater numbers of viable cells. Likewise, adhesion of EECs was also improved by grafting of fibronectin, an adhesive protein, on to PLLC scaffolds via aminolysis [49]. Such scaffolds also showed accelerated epithelium regeneration, enhanced mitochondrial activity of the EECs and increased collagen synthesis.

The next step in the evaluation of tissue-engineered oesophagus is implantation in the small animal model to assess survival of the construct, tissue regeneration and neovascularisation. Human EECs were cultured on the surface of a collagen gel, embedded with a PLGA mesh [50, 51]. The mesh was then sutured into a tubular structure with the hEECs on the luminal surface. Tubes were implanted in the latissimus dorsi muscle flaps of athymic rats. Rats were sacrificed at intervals from 4 to 28 days and studied histologically. After 8 days, fibroblasts infiltrated from the muscle, and within the collagen layer, neovascularisation could be observed. The epithelial layer continued to grow in thickness until resembling human oesophageal epithelium. Finally, staining for laminin confirmed the presence of a basement membrane.

An alternative strategy to the isolation and culture of the individual cell types is the use of organoid units. Organoid units are multicellular units containing a mesenchymal core surrounded by epithelium obtained through enzymatic digestion and mechanical agitation. In the rat model, polymers seeded with organoid units were cultured in an omental fold, followed by interposition of the polymer/organoid unit construct into an oesophageal defect [52]. The implant sight showed oesophageal tissue similar to that of native oesophagus, with a keratinised stratified squamous epithelial layer. A muscularis layer was present and stained positive for α-actin smooth muscle; however, the development was less than that of native oesophagus, with separate slips of muscle rather than a continuous layer.

As mentioned previously, the evaluation of constructs is traditionally conducted by histology after removal from the implant site. In order to evaluate the constructs in vivo, new techniques need to be employed. One such technique is that of in vivo microcomputed tomography (micro-CT). Tissue-engineered oesophagus constructs were imaged using micro-CT following implantation in rat, allowing for localisation of the position of the construct and construct dimensions [53]. In addition the surrounding tissue could be evaluated for inflammation, cyst formation and fluid formation. As in vivo micro-CT is a non-invasive method, the evaluation can be repeated at various time points to record the progress of tissue regeneration and allow comparison between different scaffold types or treatments (Fig. 32.6).

Whilst the small animal model is of importance in the initial evaluation of tissue-engineered constructs, it is limited by a lack of relevance to the human situation and the complicated nature of anastomosis procedures in such small animals. The most recent research has begun to transfer lessons learnt in vitro and in vivo, to large animal models, in particular the ovine, canine and porcine models which are of greater clinical relevance.

The large animal model can be used to reproduce partial defects, e.g. ulcers, or full thickness, patch and long-gap defects, e.g. oesophageal

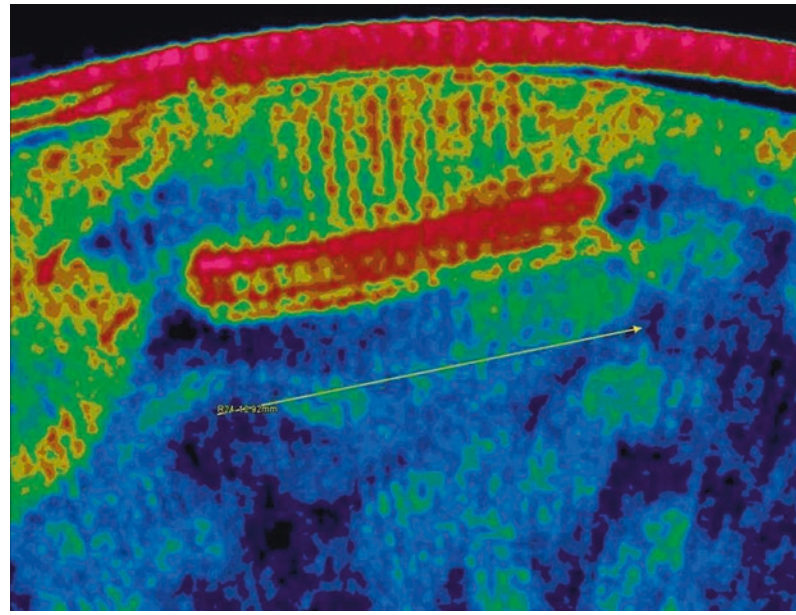

Fig. 32.6 Respiratory gated microcomputed tomography enables long-term evaluation of cell-scaffold constructs implanted in the omentum of small animals without sacrificing them. Image demonstrates a tubular stented construct in the rat abdomen 4 months after implantation

atresia. In the canine oesophageal ulcer model, tissue-engineered cell sheets were transplanted on to the underlying muscle layer at the ulcer site [54]. In cell sheet tissue engineering, cells are cultured in vitro on temperature-responsive tissue culture dishes. After forming a cell sheet, the temperature is reduced and the intact cell sheet may be removed. In the aforementioned study, cell sheets were created from canine oral mucosal epithelial cells. The transplanted sheets adhered to the underlying muscle layer resulting in complete healing and no observable stenosis. This was in comparison to the untreated oesophagi which showed fibrin mesh, inflammation and only intermediate stages of wound healing.

Whilst in this model, cell sheet tissue engineering without the use of a scaffold material has significant promise, in cases of full-thickness defects, a scaffold material is almost certainly required to provide structural support and guide tissue regeneration. In tissue engineering of the oesophagus, decellularised tissues have been the predominant scaffold material used in large animal model studies.

Small intestine submucosa (SIS) seeded with oral mucosal cells was used in the repair of patch defects in the canine model [55]. Patch defects, 5 cm in length and 50 % of the circumference, were created in the cervical oesophagus. Oral mucosal cells were isolated by separation of the epithelial layer through treatment with dispase, followed by dissociation of the cells from the epithelium with trypsin/EDTA. Cells were expanded in number through a series of passages followed by seeding onto single-layer SIS scaffolds. After 1 week of in vitro culture, the cell-seeded SIS and cell-free SIS were sutured across the defect and left for 4 and 8 weeks. The oral mucosa epithelial cells showed well spread morphology and covered the entire SIS scaffold after 1 week in vitro culture. After implantation, no serious complications were seen in either group. Dogs treated with SIS with oral mucosa epithelial cells showed a smoother lumen surface and a quicker regaining of weight in comparison with those treated with cell-free SIS. After 4 weeks, histological examination showed that the group treated with SIS with oral mucosa epithelial cells had a well-developed epithelial lining with only slight inflammation, whilst the cell-free SIS showed partial epithelial coverage and a large number of inflammatory cells. After 8 weeks, numerous long bundles of skeletal muscle had extended to the graft from surrounding muscle in the SIS with oral mucosa epithelial cells; however, in the cell-free SIS, many new blood vessels had formed,

yet few skeletal muscle bundles had extended onto the graft. No nerve fibre regeneration was observed; however, this was likely due to the relatively short duration of the experiment.

Human amniotic membrane has also been used as a scaffold for oesophageal tissue engineering, in this case, for repair of a 3-cm gap defect also in the canine model. Amniotic membrane was decellularised by treatment with EDTA and gentle scraping, was seeded with a mixed suspension of canine oral keratinocytes and fibroblasts and was cultured in vitro for 1 week [56]. After culture, amniotic membranes seeded with cells were sheeted on a polyglycolic acid (PGA) felt containing minced smooth muscle tissue, resected from the anterior wall of the stomach. The scaffolds were rolled around a polypropylene tube and wrapped within the canine omentum. After 3 weeks of abdominal implantation, the scaffolds were moved up, through the hemidiaphragm, into the thoracic space as a pedicle graft. The oesophageal defect was created and replaced with the tissue-engineered construct. The results show that after 1 week of in vitro cell culture, keratinocytes organised into a stratified layer upon the amniotic membrane whilst fibroblasts penetrated within. After the 3 weeks of abdominal implantation, the majority of constructs showed a well-differentiated luminal surface with smooth muscle-like tissue. In a small number of cases, degradation of keratinocytes and desquamation were observed. Finally, 1 week post-oesophageal replacement, strictures developed in the dogs treated with cell-free amniotic membrane control. In contrast, animals treated with the amniotic membrane seeded with cells showed no problems with passage and feeding, except for two cases of strictures which correlated with the cases of epithelial desquamation. The oesophagus in the tissue-engineered group was capable of transferring food to the stomach via peristalsis; however, there was an absence of peristaltic activity in the tissue-engineered oesophagus segment itself.

The porous areas of decellularised tissues result from the extraction of cells; however, such pore sizes are often inadequate for the ingrowth of microvessels after implantation [57]. Treatment with acetic acid and collagenase can be used to enlarge pore sizes and improve vascular ingrowth, although such treatments can also be detrimental to the stability of the tissue.

Other than decellularised tissue, few scaffold types have been applied to oesophageal tissue engineering in the large animal model. Recently, collagen sponges have been reported in the creation of a rudimentary oesophageal conduit in the adult sheep model [58]. The aim of this experiment was to create a hollow tubular construct similar in structure to that of the native oesophagus. Highly porous collagen sponges cross-linked with glutaraldehyde and preseeded with fibroblasts were seeded with cultured ovine oesophageal epithelial cells (OEEC), followed by a period of 48 h in culture to allow for cell attachment to the scaffolds. The constructs were then draped over sterile stents and closed by gently tying three Vicryl sutures looped around the construct (Fig. 32.7). The size of stent (an endotracheal tube) was matched to that of the native oesophagus to ensure the formation of a conduit with appropriate dimensions. The constructs were implanted into the omentum of adult sheep to promote vascularisation. Without a sufficient blood supply, implanted constructs will quickly become necrotic. Strategies for promoting neovascularisation of tissue-engineered constructs include fabrication of scaffolds combined with angiogenic factors, coculture with endothelial cells and implantation into an in situ bioreactor. The omentum is a highly vascular, fatty tissue, which has been used to provide vascular ingrowth in ischemic tissue and avascular grafts [59, 60]. As such, the omentum is well suited as an in situ bioreactor for tissue engineering of the oesophagus.

After a period of 8 and 12 weeks post-implantation, the constructs were removed for histological examination. The stented construct was well integrated within the omentum. After 8 weeks post-implantation, vasculature branches were observed developing around the construct. Cellular and vascular ingrowth was observed within the porous structure of the collagen scaffold, and no inflammation was noted (Fig. 32.8a). Also, OEECs were detected in patches along the

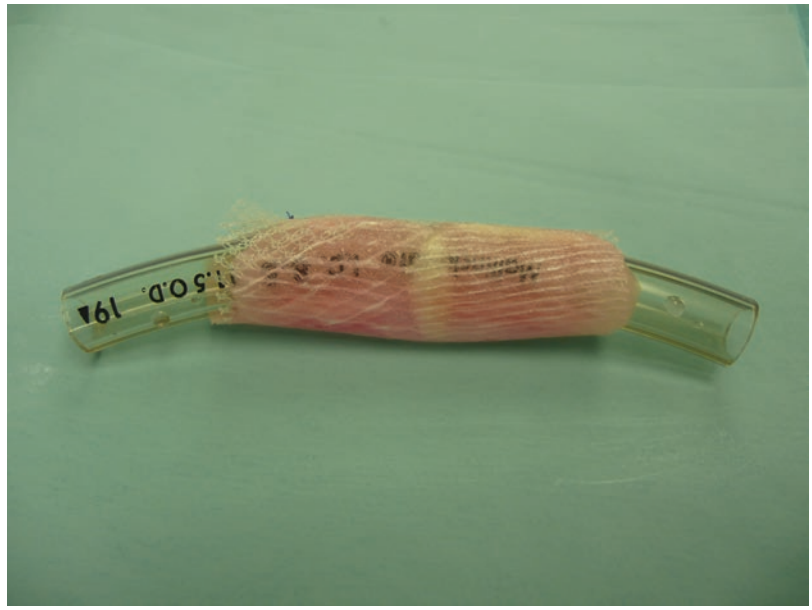

Fig. 32.7 Scaffold seeded with cells and sutured around a stent to create a tubular construct for in vivo or in situ implantation

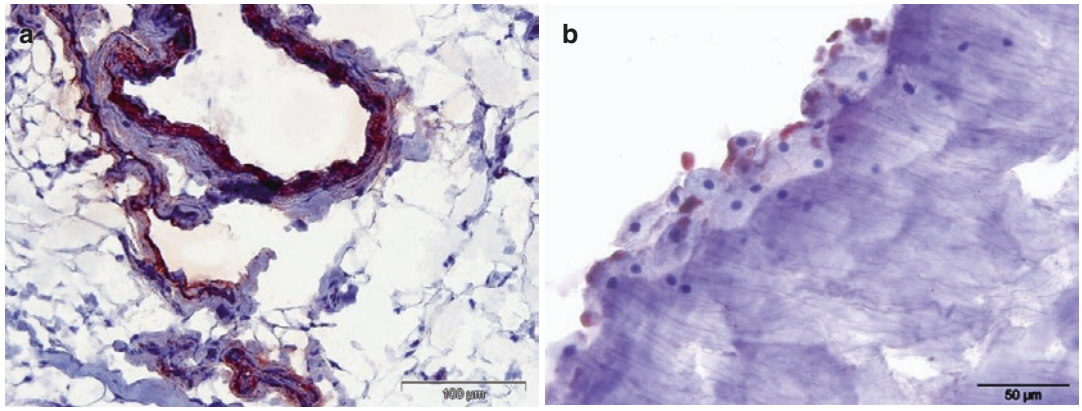

Fig. 32.8 (**a**) Vascular ingrowth into the implanted stented construct was evident at the time of explantation. Image demonstrates the immunohistochemical identification of vessel through smooth muscle actin and von Willebrand factor markers. (**b**) The luminal surface of the constructs demonstrated patches of ovine oesophageal epithelium. Image shows the inner layer of construct with ovine epithelium marked with pan-cytokeratin-26 markers

construct (Fig. 32.8b). By 12 weeks post-implantation, the implant demonstrated a hollow tubular tissue with a smooth inner lining similar in morphology to that of the native oesophagus (Fig. 32.9).

In the above-mentioned study, the scaffold was sutured to create a tubular structure. Tubular scaffolds can also be fabricated [61]. Whilst prefabricated tubular scaffolds benefit from the avoidance of suturing, and the convenience with which that entails, cell seeding of prefabricated scaffold tubes is technically difficult, accounting for low seeding densities and limited scaffold coverage. In the suturing of scaffolds for oesophageal tissue engineering, the selection of appropriate suture type and technique is of importance. The efficacy of different suture materials and techniques were investigated for porous 3D collagen scaffolds [62]. Collagen scaffolds, in both dry and wet states, were sutured using braided and monofilament sutures by continuous loop, interrupted loop, interrupted edge and continuous running edge sutures. It was observed that the suturing of dry scaffolds leads to tears during

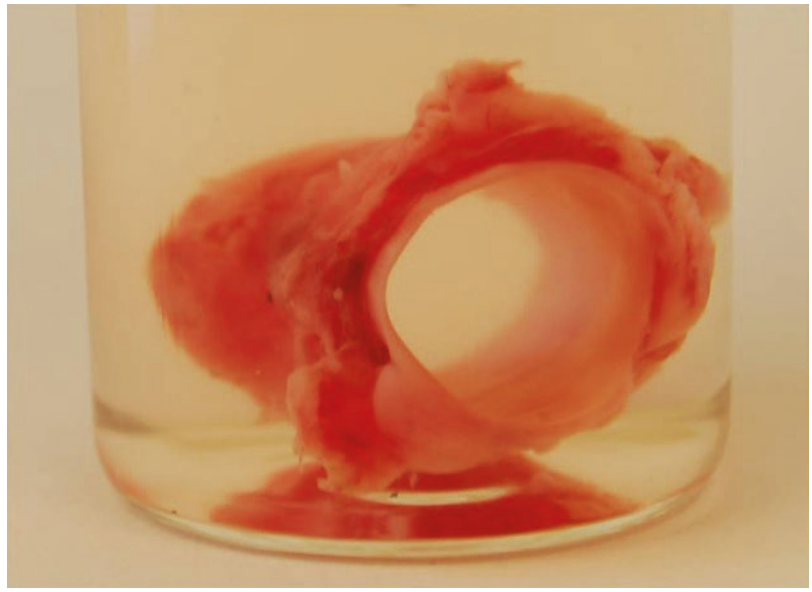

Fig. 32.9 Tubular construct after removal from the ovine omentum demonstrating the morphology of the rudimentary tissue-engineered oesophagus

knot tying and fractures when draped around a stent. Braided sutures caused friction during suturing resulting in tearing in both the wet and dry states, whilst continuous and interrupted loop suturing were limited by poor approximation of edges strangulation of the scaffold in the area of loop positioning, crushing of microarchitecture and distortion of scaffold morphology. Suturing of pre-wetted scaffolds with monofilament sutures using both the interrupted and continuous running edge suture was the most suitable technique, resulting in undistorted scaffold morphology with excellent edge adaptation. Between these two techniques, the continuous edge running suture was favoured due to the minimal use of suture material, which may avoid adverse tissue reactions [63].

Whilst many advances have already been made in tissue engineering of the oesophagus, further research is necessary, and a number of key obstacles need to be overcome. There is a requirement for development of a new generation of hybrid scaffolds and the application of stem cells. The continued increase of in vitro studies should be matched by an increase in the number of large animal model studies to allow for greater feedback for the polymer scientists and cell biologists. Finally, current tissue-engineered constructs remain as passive conduits, and therefore, future work must focus on the development of a functional construct, with a neurogenic component, that may become integrated into the peristaltic activity of the oesophagus.

Conclusion

To summarise, tissue engineering offers great potential for oesophageal replacement. Future research will focus on the improved design of scaffold materials for guided tissue growth and organisation, the development of protocols for the isolation, proliferation of oesophageal and stem cells and the optimisation of devices for prolonged in vitro culture [64]. Present research has enable generation of rudimentary forms of oesophageal conduits; however, enormous work and resources are still necessary to replicate and generate a functioning oesophagus.

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Part VIII

After EA-Repair: Complications and Post-repair Issues

Overview: The Post-repair Issues and the Active Pursuit of Normalcy

33

John E. Foker

Introduction

The goal of this book is to help patients with esophageal and gastric disorders realize 70 or more good years, an admittedly stringent requirement. When starting life with a congenital defect as severe as esophageal atresia (EA), this goal is even more difficult to attain. The majority of patients with EA and a distal tracheoesophageal fistula (EA/TEF) have a shorter gap allowing an outwardly successful primary repair. Consequently, they are generally thought to be "getting along well." The longer-term follow-up reports, however, from Finland, the Netherlands, and Canada as well as smaller studies have revealed that many of these patients have related, residual problems [1–16]. In these series, the adult patients who had EA/TEF repaired as infants were often found to have dysphagia and/or the consequences of gastroesophageal reflux (GER), potentially significant obstacles to the goal of 70 good years (see also Chaps. 50: "Long-Term Follow-Up of EA/TEF Patients" and 52: "Follow-Up of EA Repair: The Helsinki Experience").

Most EA/TEF patients, nevertheless, believe they are doing well in terms of quality of life (QOL) unless these difficulties clearly impact on their well-being [3, 7, 9]. The generally positive responses to QOL questions by EA/TEF patients are similar to the relative optimism found in similar surveys of patients with other serious, chronic diseases. Despite this favorable opinion of their lives, many EA/TEF patients have significant problems both early and over the longer term which, in many cases, could be assessed and treated, improving the actual QOL.

The outlook is even less favorable, however, for infants who either began with a long gap (LG) between the esophageal segments or had a failed EA/TEF repair which converted a short-gap EA to a long-gap problem. Patients, with either primary or secondary long gaps, comprise the difficult end of the EA spectrum and pose great difficulties for the pediatric surgeon.

Currently, a patient with a moderately long gap which is felt to preclude a true primary repair may have some combination of esophageal myotomy and/or partial gastric pull-up to make an anastomosis possible. If the esophageal defect is even too long for that approach, continuity will be established when the child is older and larger, usually by either a gastric pull-up or a colon interposition graft. These solutions allow the LG child to eat, but, interpositions are not functionally reliable and the problems with them typically

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increase in number and severity with time, making it unlikely that the long-term goal (70+ good years) will be reached.

We have presented, in contrast, the surgical approach which will induce catch-up esophageal growth so that both primary and secondary LG-EA patients can have a true primary repair with no myotomies and the GE junction below the diaphragm [17–20]. The resulting, newly grown esophagus appears normal structurally and has allowed a primary esophageal anastomosis to be reliably achieved. Overall function which includes lower segment dysmotility is, nevertheless, satisfactory and has resulted in normal eating [20–22] (Table 33.1) (see Chaps. 25 "Growth Induction"; 40 "The Reoperation").

Follow-up studies of the LG-EA patients have indicated that they may also have related problems such as GER and dysphagia which can produce difficulties. Consequently, we have actively pursued normalcy in the early postoperative period by assessing and treating any remaining repair-related issues. By this active approach, the potentially long-term problems can be identified and largely prevented from producing chronic disease.

Our working hypothesis has been that if the problems following a primary LG-EA repair are effectively treated early, they will be less likely to persist or even reappear later. This approach may also have value for a patient with the much more common EA/TEF repair who has one or more related problems. With an active follow-up and effective treatment of any difficulties that appear weeks or even months after repair, we believe the patient's QOL from an esophageal standpoint should remain favorable far into adulthood.

Table 33.1 Growth induction follow-up

External traction (initial gaps 5.8 ± 1.9 cm)	
Questionnaire answers (28/36 returned)	
Results >3 years after primary repair	
Eat normally for age	27/28
Occasional g-tube supplementation	3/28
PPI medication	5/28
Possible reflux	4/28
Pulmonary symptoms	0/28

Problems After a LG-EA Primary Repair

The considerable advantages in eating for LG-EA patients following a primary esophageal repair are clear. The growth method, however, may have postoperative problems that deserve attention. Roughly in order of frequency are gastroesophageal reflux (GER), strictures, and aspiration (pulmonary problems), as well as nutrition, airway, and skeletal issues which may complicate the outcome of the growth approach for LG-EA [17–20]. Reflux and strictures are the most common and, if untreated, are likely to produce problems even into adulthood. Consequently, we carry out early evaluation and any necessary treatment to prevent the patients from slipping into a state of chronic illness.

Aspiration may result from any combination of GER, strictures, an aperistaltic colon or gastric interposition graft, or the presence of a residual or untreated pouch in the tracheal membranous septum. The consequences of aspiration may be serious either acutely (pneumonias) or chronically by producing significant lung injury. Chronic lung damage can be insidious as well as a serious consequence. Whenever suspected, the presence of aspiration should be assessed, and the cause, if found, should be effectively treated.

There are other possible problems that are also secondary in nature. Continuing gastrostomy tube feeds may be necessary to avoid malnutrition until eating by mouth becomes established. Airway problems may be significant, and even moderate tracheomalacia can lead to air hunger and apneic spells. Skeletal problems can be acquired, usually from sequelae of the thoracotomy incisions or may be congenital in origin such as the vertebral and rib anomalies.

The great majority (>90 %) of LG-EA patients that came to Minnesota already had one or more failed attempts at repair, further complicating what was required to eventually achieve normalcy. These patients came from many other centers which also revealed that wide variation exists in the diagnostic criteria for these issues and in the treatment plans for them. GER and strictures occur in a spectrum of severity, and the clinical

variety was matched by the differences in judging their significance as well as in the therapies formulated. The same diagnosis and treatment variations were found regarding aspiration, pulmonary issues, and the consequences of tracheomalacia which may occur after LG-EA repair. Add to these the differing experience and capability of the practitioners, and it is understandable why therapies vary widely and meaningful comparisons of results are difficult.

The purpose of this chapter, therefore, is to present our approach for the LG-EA patient after a period of growth and a primary anastomosis. Our approach, which was developed at the University of Minnesota, evolved to meet the circumstances and problems encountered and was not derived from evidence-based medicine. The variety and complexity of these patients would certainly defeat any attempt at controlled studies. The final judgments about our approach, however, will only come with the passage of considerably more time as the longer-term results become apparent. Nevertheless, the results to date of the early identification and active treatment of related issues have been very encouraging with the great majority of our LG-EA patients eating normally and free from most residual symptoms [19, 20] (Table 33.1).

Gastroesophageal Reflux

Following LG-EA repair, GER is the most important complication because of its common occurrence, frequent severity, and difficulty in achieving effective control despite the many treatment options. The concerted efforts among acknowledged experts to set up guidelines for GER evaluation and treatment, notwithstanding, a relatively uniform approach has not emerged and local methods and individual experience often dominate [23]. As a result, there has been a surprising lack of consistency across centers in deciding how much GER is too much and how it should be treated.

Even during the esophageal growth period, reflux into the lower esophageal segment could be injurious and produce ulcerations. Reflux was minimized, therefore, by keeping the patients on hyperalimentation for nutrition and by elevating the head of the bed to at least 30°. Proton pump inhibitors (PPIs) were given to reduce the acid content (the gastric pH was kept greater than 5), although bile reflux could not be prevented. Following the primary anastomosis, this regimen was usually maintained until the decision regarding a fundoplication was made. After the fundoplication, oral feeding, more accurately, the efforts to encourage learning to eat, was promptly begun and usually the antacid therapy (PPI) continued for another 1–2 months. Once back in the home area, PPI therapy might be continued without clear rationale.

There are structural and functional reasons why GER is almost always significant after a primary repair of LG-EA. The lower esophageal sphincter (LES) often appears to be virtually absent as an anatomic and functioning unit prior to growth induction. Initial contrast studies frequently show the distal esophagus to be broad based without any narrowing above the stomach, suggesting a physiologic GE junction is not present (Fig. 33.1). And, at the most extreme end of the EA spectrum, the lower segment may be nothing more than a primordial nubbin with an uncertain potential for

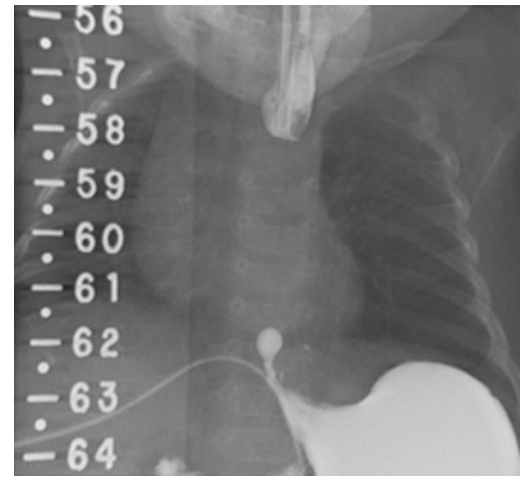

Fig. 33.1 Contrast study of long-gap esophageal atresia prior to growth induction and repair. The lower esophageal segment is notable for a very broad base at the junction with the stomach, suggesting very little or no functioning tissue which would hinder reflux

developing a structural GE junction (see Chap. 25: "A Flexible Approach", Figs. 14a and 15a, b). Axial tension will reliably induce growth and produce a structurally outwardly normal lower esophagus; however, nothing is known about its effects on the development of a functional GE junction [21, 22].

The development of a barrier to GER takes 5–7 weeks after birth even in the normal child. The well-described motor dysfunction of the lower esophagus after straightforward EA/TEF repairs allows increased reflux, and, in one study, the incidence of GER continued to increase for at least 3 years following repair [6, 9, 10, 24–27]. It is unknown whether or not a functional GE junction would develop even over a much longer time period in LG-EA patients following growth induction [23]. Based on the degree and frequency of GER after a primary LG repair, it is likely the specialized area of the gastroesophageal sphincter would, at best, be very slow to develop.

For virtually all repaired EA patients, whether long or short gap initially, the peristaltic wave which begins in the cervical esophagus does not pass through the anastomotic site. Normally, peristalsis is largely propagated within the syncytium-like muscular layer and is easily stopped by nonconducting fibroblasts and myofibroblasts at the anastomotic site. Furthermore, what segmental vagal innervation is present in the lower esophagus is not sufficient to reliably restore effective peristalsis below the anastomotic line. Esophageal function below the anastomosis, or below the highest myotomy, will typically consist of only sporadic contractions on manometry studies. In addition, because of the dysfunction, there will be little barrier to reflux, and the ability to clear the lower esophagus will also be impaired [25–28].

There are three main consequences of GER, of which progressive inflammation leading eventually to Barrett's changes is best known [1, 28–34]. Unchecked, the metaplastic changes described by Barrett are precancerous, and reflux, as a type of environmental carcinogen, can begin to result in cancer forming about 15–20 years later. Because of the importance of this detrimental progression, it has been well described in other chapters (Chaps. 72: "Pathophysiology" and 73: "The Esophageal Mucosa").

The other two consequences are also of importance to EA patients and infants in general. Significant GER may reach well above the level of the carina making aspiration likely. Pulmonary symptoms and even infections may be the most important consequence requiring fundoplication in infants with or without EA [35–41]. Pulmonary symptoms from aspiration in EA patients may also result from strictures, tracheomalacia, or a recurrent diverticulum or fistula. The presence of pulmonary problems requires a careful evaluation to establish and effectively treat the cause.

Finally, GER also produces an unpleasant sensation which the infant cannot verbalize but often responds to by refusing to eat. GER may, therefore, be an important component of oral aversion. Although the discomfort of GER is usually reduced by antacid therapy, bile may also produce a less symptomatic inflammation and the sensation of reflux often remains [28, 31, 33]. Learning to eat may also be complicated by the presence of a stricture with dysphagia. These adverse functional consequences of repaired EA, as well as the fact that the instinct to eat has faded, are more than enough reasons why learning to eat can be slow and difficult.

The connection must be made between being hungry and eating. The presence of one or more of these negative functional components, together with a vanished instinct to eat, may make efforts to teach taking and swallowing of food arduous. Why one should put food in one's mouth is not obvious and if it does not pass easily into the stomach and/or brings the unpleasantness of reflux, it may be resisted. Oral aversion would seem to result from some combination of these factors, rather than being a specific mechanism.

Establishing the connection is greatly helped by stopping gastrostomy feedings for 2 or more hours before offering liquids by mouth. Nighttime infusions by g-tube should be stopped at least 4 h before the morning attempts at oral feeding. They need to be hungry for the connection to be made. Patience will be required for the many attempts

needed, but once the connection is made, our experience has been that the learning usually proceeds very quickly and the children will soon dislike g-tube feeds (see Chap. 45: "Learning to Eat After EA Repair").

All of these issues, if linked to GER, we believe, make a strong case for an anti-reflux procedure (usually a fundoplication). The GER will be controlled and the consequences eliminated. In addition, if necessary, feeding through the gastrostomy tube will be more easily available to prevent malnutrition.

Fundoplication After LG-EA Repair

The LG-EA patient after primary repair usually presents a difficult problem, both in the severity of the GER and in achieving effective and durable surgical anti-reflux treatment. A primary repair of a true long-gap lesion, even after a period of induced growth, may still require an anastomosis under some tension. As a result, the GE junction will usually be pulled up tightly against the diaphragm at the hiatus, hindering creation of the fundoplication.

GER in LG-EA patients, as opposed to otherwise normal infants and after most EA/TEF repairs, will be unlikely to resolve on its own; consequently, we have favored early evaluation and treatment [6, 18, 19]. LG-EA patients were studied about 3 weeks after the primary repair by an esophagram done in a semi-upright position to assess both the anastomotic site and the amount of GER. If free reflux to the carina and above was present on the contrast study, we usually recommended a fundoplication. Although early fundoplication precluded determining whether or not the GER would resolve on its own, a functional LES seemed unlikely to eventually develop [16, 19]. The incidence of significant GER has been observed to double from 6 months to 1 year following EA/TEF repair and was greater than 50 % after 5 years [6]. Not only would a wrap reduce the inflammation and stricturing effects, it would also remove the reluctance to learn to eat.

We realized the standard approach would be to wait much longer before recommending a fundoplication; however, a wrap solved these post-repair issues and put the patient and family on the path to normalcy. Our approach also avoided long-term medical GER treatment which incurs significant cost, requires continuing clinic visits, may have side effects such as bone and muscle weakness, and, very importantly, conveys to the child and family a state of chronic illness [42–46]. Furthermore, the adverse consequences of GER are often difficult to determine by symptoms, potentially giving a false sense of security [47]. The seriousness of Barrett's changes over 15–20 years should not be doubted, however, as even cancer of the cervical esophagus has occurred in gastric pull-up patients.

A fundoplication in EA patients, however, might produce its problems. The wrap tends to create a partial obstruction, which may, potentially, further decrease effective esophageal function and the ability to eat. As with adult patients, a partial wrap has been advocated to avoid producing a degree of obstruction [48]. We, and others, have found that a more common problem with fundoplications is that the wrap may loosen with time and has been reported to become ineffective in about 33 % of EA patients [49–52]. Although paraesophageal herniation has been cited as the most common reason for the failure of fundoplications, we have found loosening of the wrap itself is, by far, the most frequent reason for recurrent reflux [52]. The reported difficulties with fundoplications both in EA patients and otherwise normal children have tempered recommending them in many centers [50–53]. Similar difficulties have also been reported with the redo-fundoplication [54, 55]. Our experience, nevertheless, has found them very beneficial to the repaired LG-EA patients even though some fundoplications were too tight initially or, more commonly, loosened later and required redoing in about 20 % of cases. These problems can be solved, allowing the substantial benefits of a barrier to reflux to emerge.

The technique of loosening a fundoplication by endoscopy will be described. For wraps that became too loose, reoperation restored the anti-

Table 33.2 Learning to eat after growth induction LG-EA repair

	LG-EA	Normals
	(*N*=21)	(*N*=26)
	Months	Months
Finger feeding	15±2 (12)	11±2 (5)
Solids with spoon	22±2 (14)	20±2 (8)
Drinking from cup	21±2 (15)	19±2 (8)
All milestones	26±2 (9)	28±2 (8)

reflux function, although in a few cases, a third wrapping was required. Despite the potential contribution to esophageal dysfunction by the fundoplication, the sporadic contractions together with the effect of gravity will result in satisfactory emptying, and for these children, eating will be normal (Table 33.1) [19–22]. Furthermore and remarkably, these children have learned to eat after fundoplication at the same rate as normal children do after birth despite the severity of their initial EA defect [20] (Table 33.2).

The principles and results of fundoplication for GER have been well presented in several chapters (see Chap. 43: "Surgical Considerations of GE Reflux Pre and Post EA Repair") and also chapters on non-EA patients (Chaps. 92: "Gastroesophageal Reflux: From a Surgeons Perspective"; 93: "The Spectrum of Surgical Anti-reflux Procedures" and 94: "Minimally Invasive Fundoplication").

The Technique of Fundoplication in LG-EA Patients

To accomplish a satisfactory fundoplication after growth induction for LG-EA, the following operative approach has been used. Through a short left subcostal incision, the left lobe of the liver is mobilized after dividing its ligaments and retracted to the right which reveals the stomach and diaphragm. After a growth procedure and later anastomosis, the GE junction and gastric fundus will usually be tight against the diaphragm, seeming to make it difficult to expose a 2–3 cm length of esophagus. The GE junction may be unapparent but can be reliably located at the very upper margin of the lesser curvature. The vagal branch to the liver and gall bladder arises at a right angle from the vagus nerve and together with a small vein crosses and identifies the GE junction and then passes over the quadrate lobe on the way to the liver hilum. This vagal branch is easily recognized and spared by keeping the dissection above it. If the wrap is done above the nerve, it will be around the esophagus and not the stomach.

To aid in bringing down the GE junction and exposing a length of esophagus for the wrap, a 4-0 or 3-0 Prolene suture is placed around the presumed GE junction by taking very superficial tissue bites just above the nerve (Fig. 33.2). The suture is tagged and placed on traction which will aid in bringing below the diaphragm a 2–3 cm length of esophagus (Fig. 33.3). The crura of the hiatus are identified and 4-0 Tevdek sutures used to narrow the opening by taking generous bites of muscle with careful tying of the sutures to avoid tissue necrosis. Pledgeted sutures are used if tissue quality seems poor. The wrap can then be constructed around the esophagus.

Sizing the Fundoplication

We prefer a relatively tight fundoplication because recurrent reflux from wrap loosening was by far the most frequent important problem that developed. To size the hiatal closure and the subsequent wrap, a nasogastric tube was passed down into the stomach; a 14 Fr nasogastric tube would be used for patients up to a year of age and a 16 Fr tube for 1 to 2 year olds.

An important reason for wrap loosening was retching caused by overfeeding through the g-tube. To minimize stress on the fundoplication, when retching first begins, the feeds were stopped and the g-tube quickly vented to decompress the stomach and remove the stimulus to vomiting. Parents were instructed to carry out these maneuvers as quickly as possible with the onset of retching to stop the forceful abdominal contractions which loosen the fundoplication.

If the fundoplication seemed too tight after attempts at feeding or even inability to swallow saliva, it was loosened, but only rarely actively

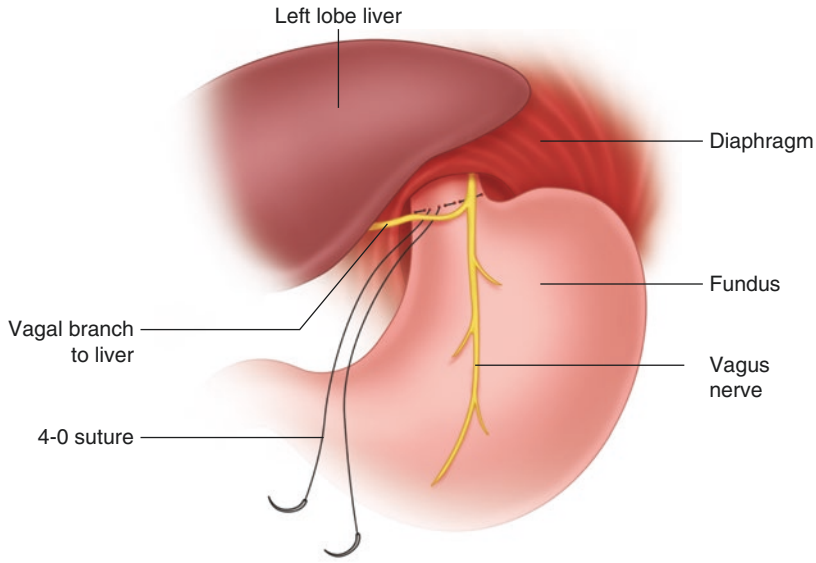

Fig. 33.2 Diagram of a stomach pulled tightly up against the diaphragm after an esophageal growth procedure and primary repair. This consequence makes a fundoplication more difficult to create. The esophagus must be dissected free and mobilized for the fundoplication. An important landmark is the vagal branch to the liver and gall bladder which crosses at the level of the GE junction. If the dissection is kept above this branch, the wrap will be around the esophagus. The first step is to take superficial tissue bites with a 4-0 Prolene suture around the esophagus above the vagal branch as shown

dilated. Under general anesthesia with an ET tube in place, an extra stiff wire was passed either up from below through the gastrostomy site or down from above through the oral pharynx to guide a smaller 6–8 mm (4 cm long) balloon. With the balloon fully inflated (4 ATM), it was pulled or pushed to cross the fundoplication. If it would not cross without significant force, the balloon was gradually deflated until it would pass. The process was repeated with the diameter of the balloon increased by 2 mm increments up to at least 10 mm. To finish the loosening, the balloon was pushed or pulled across the fundoplication one last time.

Most of the time, with the first attempt, a 10 mm balloon was able to be pulled or pushed through the fundoplication, even in very young children. A smaller balloon was only used when the distal esophagus was smaller than 10 mm in diameter. The amount of force used to push or pull a balloon through the fundoplication was subjective, although more force was needed pushing from below. It might take 10–20 s pulling/pushing on the balloon before it would slide through, particularly with a recently constructed fundoplication. Very occasionally, the balloon was inflated within the fundoplication to dilate it, but only when the amount of force required to pull it through seemed too great.

These simple techniques have proven surprisingly effective in slightly loosening, but not disrupting, a too-tight fundoplication. This method was devised and routinely carried out successfully by Charles Dietz MD, Chairman, Department of Radiology, University of Minnesota Medical School.

Anastomotic Strictures

There are several reasons why a stricture develops at the anastomotic site. The circular nature of the anastomosis sets up the geometry of a stricture, and healing will necessarily be accomplished by myofibroblasts. For the LG-EA patient, tension on the anastomotic site is often present, and the distractive forces would logically make a thicker ring of healing with greater potential for contraction.

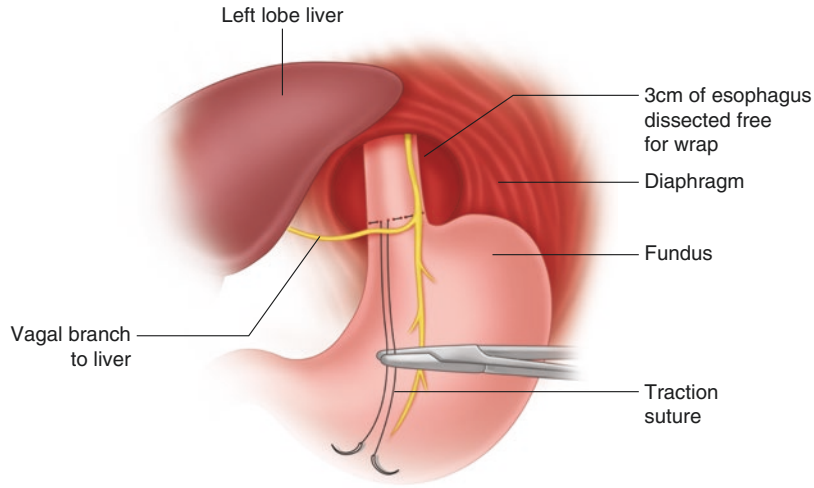

Fig. 33.3 The circumferential suture is tagged, and with downward traction, the lower esophagus is dissected free as shown. When a 3 cm length is freed up, the hiatal opening is reduced by suturing the crura and a standard wrap carried out. The smaller hiatus keeps the wrap and GE junction within the abdomen. The traction suture is removed

Tension on the anastomotic site may also produce an effect resembling a finger pull toy in which pulling on each end narrows the center, reducing the diameter of the anastomosis.

The much greater tendency of LG-EA patients to develop GER will also lead to increased inflammation and fibroblast differentiation at the site. The healing anastomosis normally contains a lot of cellular activity which will be increased by the cytokine products of inflammation. Cytokines trigger fibroblast differentiation into contractile myofibroblasts which also lay down a contractile collagen; both contribute to building a stricture. With the anastomosis under tension, and somewhat distracted, a longer time will be also needed until the area is covered with mucosa and the inflammation reduced.

All of the preceding factors tend to produce a stricture which narrows the lumen (see Chap. 37, "The Biology of Stricture Formation").

The Treatment of Strictures

The goal of therapy is to both reverse the obstructive narrowing and allow the structuring process to relent which it will naturally do as the stimuli recede. A durable, generous sized anastomotic site should be the result. Dilations were usually begun after the GER was controlled by a fundoplication because effective treatment of a stricture is difficult if significant reflux is present. Although one must respect the recently constructed anastomosis, we began to gradually enlarge it by very gentle balloon dilations as soon as 3 weeks after primary repair. Early, before dense scarring develops, the anastomotic area can be more stretched than split.

The mucosal layer, however, may not be intact at the site, and the dilations should avoid disrupting the ingrowing mucosa as much as possible. Traditional push-through dilators of the Maloney or Savary type produce a shearing action, denuding the area more than a carefully done balloon dilation. By adjusting the balloon pressure during inflation, the vigor of the dilation can also be modified, making the mucosal injury less. These considerations favor more frequent (weekly or biweekly) but less vigorous dilations which will allow a normal contour to be achieved without excessive splitting and scarring of the esophageal wall and with minimal disruption of the mucosal layer.

If one waits to dilate until the patient becomes symptomatic and the lumen quite narrow, then one is, in effect, starting over each time and the dilation must necessarily be more traumatic.

An incremental and less damaging enlargement of the anastomotic site will allow the stricturing tendency to relent while slowly increasing the lumen diameter. To begin the dilations, a 10 mm balloon was passed through the anastomosis or it

would be dilated first. The balloon diameters were gradually increased until they were 2–3 mm larger than the esophagus above and below the strictures. The over-dilation will allow the esophagus to accommodate passing solids normally. By continuing the dilations until the esophageal lumen was normal in contour and remained stable, the patients were commonly free from even mild stricture symptoms [19, 20]. Stability of the anastomotic site opening can be demonstrated by a contrast esophagram done 2–3 weeks after the last dilation.

For the more difficult strictures, other methods are evolving. The short-term placements of stents, the use of the dynamic stent, and even incisions with a cutting cautery knife are showing promise. In addition, injections with steroids or mitomycin C may be used, although their effect seems limited. These methods are continuing to evolve and their value will be expected to increase with time (see also Chaps. 38: "Pathobiology and Treatment of Strictures" and 39: "The Dynamic Stent").

Not all strictures, however, will respond completely to these measures alone or in combination. During this time, the patient will be out of the hospital and returning for the dilations; nevertheless, these procedures and the stricture itself may interfere with the child's overall progress and certainly will convey an image of chronic illness. Dilations should not be continued indefinitely without signs of improvement. The judgment of how much swallowing difficulty should be tolerated will not be uniform among practitioners nor will the treatment recommendations. The decision that a stricture is truly recalcitrant and treatment will not be effective no matter how long it is continued will vary from center to center.

The stricture should either relent after a number of dilations or it may make sense to recommend resection. This decision will depend on the length and severity of the stricture, the experience and capability of the surgeon to carry it out, and, of course, the willingness of the family to have another operation performed.

Anastomotic strictures are typically relatively short in length (1.0–1.5 cm), and the esophagus above and below will have grown sufficiently so the reanastomosis can be generous in size and the resulting tension mild or, at most, moderate. It is important to realize, however, that the esophageal ends will retract and what was visualized to be a 3 cm gap will be 6 cm in length. This predictable gap increase has led to the frequent use of additional, undesirable methods such as partial gastric pull-ups and circular myotomies to make the anastomosis less daunting.

For the long stricture, growth induction of the normal esophagus above and below by a staged growth procedure has been very effective even for lesions seemingly beyond the possibility of complete resection and primary repair. Resection of a stricture, whether short or long, requires sufficient surgical expertise to achieve a satisfactory result (see Chaps. 41: "The Redo Operation" and 42: "Growth Induction for Long Strictures").

Once the stricture resection and reanastomosis is accomplished, a series of postoperative dilations will be needed beginning 2–3 weeks later. The circular anastomosis after the resection will also have a tendency to contract; however, only two to three dilations are typically needed after complete resection for a stable result.

Aspiration

Aspiration is an important symptom with more than one potential cause in LG-EA patients. Anything which interferes with esophageal emptying will cause backup and aspiration leading to acute problems including pneumonia and, importantly, to chronic lung damage. There are several possible causes including significant GER, a stricture, or a residual tracheal diverticulum, and more than one may be operative. GER is a well-known cause of aspiration and pulmonary problems even in normal infants [35]. Aperistaltic, dilated colon, and gastric interposition grafts are among the causes most likely to produce significant lung injury with severe long-term consequences. Because of its seriousness and the various possible causes, the presence of aspiration should lead to a systematic evaluation to arrive at an appropriate treatment plan. Again, it is a serious symptom, capable of significant injury and problems and when present requires attention.

Airway and Skeletal Problems

Several airway and skeletal problems are associated with LG-EA lesions and repairs. Tracheomalacia, presumably caused in part by the dilated upper pouch of EA, is well known. The presence of a diverticulum in the posterior tracheal membrane, whether an isolated anomaly or left after an EA/TEF repair, may also produce significant infectious pulmonary consequences.

Because of the specialized nature of these problems, they have been covered in specific chapters (see Chaps. 12: "Skeletal Anomalies"; 40 "The Redo Operation"; 46: "Apparent Life Threatening Events" and Cossi; 49 "Tracheomalacia and the Effective Aortopexy").

Summary

Our continuing follow-up studies support this active overall treatment plan. All patients who have returned for our ongoing evaluation ($n = 15$) had a normal esophageal contour, and the anastomotic line was not discernible (Table 33.3). Importantly, these children generally eat whatever they wish and do not need to cut the food into tiny pieces. By questionnaire, 27/28 parents said their child eats normally and has no signs or symptoms of swallowing difficulty (Table 33.1).

These results do not prove this treatment plan should be followed; however, it certainly provides evidence for its value. All of the LG-EA patients had very long gaps initially, and a period of external traction and growth was necessary to allow a true primary repair. Despite the time required to achieve adequate esophageal growth and later to resolve the various issues, the patients were on a path to normalcy in terms of their esophageal defect. The children will not remember the procedures and treatments, although the parents will. Without growth induction and the development of an outwardly normal esophagus, they would have faced a very uncertain future.

We have acknowledged this approach was developed without controlled studies; however, it has been based on the observation and treatment of many patients. The result has been that the great majority of Minnesota LG-EA patients are of acid-inhibiting medications, are able to eat at a normal pace, and are free from long-term stricture-related symptoms (Table 33.1) (Chap. 52: "The Minnesota Experience with LG-EA"). Very importantly, they do not carry the emotional and developmental burden of chronic illness with frequent clinic visits, juggling of medications, and somber discussions about their current health.

Table 33.3 Growth induction EA repairs clinical evaluation ($N = 15$)

Traction method: external 12, internal 1, both 2	
Esophagram	
Normal contour	15/15
Endoscopy	
Gastric mucosa >2 cm above LES	2/15
No visible esophagitis	15/15
Appearance normal	15/15
Biopsy: mild esophagitis	2/15

Even though the defects of esophageal atresia (EA), and especially LG-EA, often pose difficult problems, solutions can be chosen which create a close approximation of normalcy. Virtually, all children from our series who are 10, 15, and more years from esophageal repair are outwardly normal from an eating standpoint. Furthermore, because the anatomic and physiological principles underlying this approach achieve, as closely as possible, the normal state, there seems to be no reason to expect later deterioration. This outlook, in contrast to more palliative solutions for LG-EA such as a gastric pull-up or colon interposition, often brings greatly increasing problems with time.

This long range view, however, may pose difficulties for the surgeon whose time line is often much shorter and aims for the patient to have a relatively quick discharge without unacceptable early postoperative complications. Unfortunately, for LG-EA patients treated by growth induction, a short length of stay will be uncommon; however, it will be the approach that places the child on a path to 70 good years. To maximize the chance of the patient reaching this goal, the guiding principle should be to make the end result of treatment as close to normal as possible.

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34 Evaluation After EA Repair: Endoscopy, Ultrasound, and Function

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Introduction

This chapter focuses on the use of upper endoscopy or esophagogastroduodenoscopy (EGD) in patients with esophageal atresia (EA), with or without a tracheoesophageal fistula (TEF). The typical indication for endoscopy is to investigate upper gastrointestinal (GI) and respiratory symptoms in patients who have undergone EA repair. Diagnostic findings may include gastroesophageal reflux (GER), esophagitis, Barrett's metaplasia, and anastomotic narrowing. Endoscopy is useful for assessment of fistulas and diverticula, estimation of lower esophageal sphincter (LES) dysfunction and/or adequacy or "tightness" of a fundoplication, or disordered motility that is seen in patients with a history of EA repair. Therapeutic endoscopy may involve dealing with food impaction, potentially addressing fistulas or leaks and management of anastomotic stenosis (covered elsewhere in this book).

We have found endoscopy to be of particular value in infants with long-gap EA (whose esophageal gaps exceed 2.5 cm) in the pre- and perioperative period. EA, with or without a TEF, is an uncommon pediatric surgical problem [1]. Most esophageal defects are small; primary repair is usually possible soon after birth. But long-gap EA is more challenging, with no single agreed-on technique for repair [2]. The methods commonly used involve either esophageal lengthening or esophageal substitution with an intestinal segment or gastric transposition [2].

Over the last two decades, we have developed a technique at our institution to salvage the esophagus in children with long-gap EA [1, 2]. Most of them have additional morphologic issues, which often need to be addressed simultaneously with their esophageal problems. Not surprisingly, a large proportion of them have type A, or pure EA, in which the lower esophageal pouch may be diminished and difficult to use for primary repair.

The technique involves traction to grow the esophagus so that a primary repair can be performed. Our overarching belief is that the patient's own esophagus should be preserved.

In this chapter, we have focused on upper endoscopy technique and important considerations in small children and how we have further adapted standard techniques in infants with long-gap EA. We use endoscopy from the initial assessment of these patients, then throughout the repair process as well as during follow-up. We also discuss the potential luminal pathologies in this patient group and how endoscopy can be useful.

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Endoscopic Procedures

Preparation

In describing the procedure, we have focused on the nuances of endoscopy in infants and small children and how it pertains to the EA population. Routine EGD in older children and adults does not differ significantly from the normal population apart from taking into consideration childhood problems that persist (as noted here). Preparing patients for any procedure requires obtaining a history and performing a physical examination and taking care to review comorbid conditions along with upper airway and respiratory status. Infants with EA may have additional issues related to the VATER (*v*ertebral defects, imperforate *a*nus, *t*racheo*e*sophageal fistula, and *r*adial and *r*enal dysplasia) complex. Asking for informed consent from the patient (or parent or guardian) is mandatory [3].

Emotional and psychological preparation of pediatric EA patients (and parents or guardians), including counseling, may help them tolerate the procedure [4, 5]. No data specifically support such preparation in EA patients; however, one study that randomly assigned some pediatric patients to psychological preparation found that they had significantly less anxiety before, and greater compliance during, endoscopy; they also required less sedation [6]. For young children, the presence of a parent until sedation begins is helpful in allaying anxiety; similarly, locally applying anesthetic skin cream before placing an intravenous (IV) line and premedicating children with oral benzodiazepines can significantly allay anxiety [7].

Before undergoing endoscopy or anesthesia, an oral fast is standard. Guidelines in the United States regarding children have been developed by the American Academy of Pediatrics (AAP) and regarding adults, by the American Society of Gastrointestinal Endoscopy (ASGE) [8]. Gastric emptying times do not necessarily correlate with fluid volume in the stomach [9]. Despite fasting, the interval before endoscopy should be a minimum of 2 h for clear liquids, in order to reduce the risk of pulmonary aspiration [10]. In patients with suspected ileus or gastric delay, precautions are needed during induction of anesthesia. Gastric emptying can be delayed in children with EA. In our population of EATEF, we have noted gastric delay in 10–15 % of infants.

Bacteremia is unusual in healthy patients undergoing diagnostic endoscopy, and children may be less susceptible [11]. In a survey of 16 North American pediatric endoscopy centers, most endoscopists restricted use of prophylactic antibiotics to patients undergoing percutaneous placement of gastrostomy tubes and to patients with moderate-to-severe structural heart disease, which is associated with a risk of bacterial endocarditis [12]. Those restrictions are in keeping with guidelines established by the American Heart Association (AHA) and by the ASGE. Bacteremia does occur with esophageal therapeutic procedures, yet it appears to be transient [13]. Antibiotics may need to be considered in EA patients undergoing therapeutic procedures, but their use must be individualized; complex cardiac defects are also an association with the VATER syndrome and a thorough evaluation of the cardiac defect is prudent prior to endoscopy.

Sedation or Anesthesia

In adults, routine upper endoscopy is rarely performed under anesthesia; instead, sedation (with careful monitoring) is standard. In children, guidelines detailing sedation and monitoring during endoscopy have been published, including by the AAP; such guidelines likely determine clinical practice, at least in the United States [5, 14, 15]. *Conscious* sedation is defined as a state in which patients retain the ability to respond to verbal commands, i.e., the respiration and protective reflexes remain intact. *Deep* sedation is a depressed conscious state from which it is difficult to rouse patients. In the typical clinical situation, a continuum likely exists between conscious and deep sedation [16]. The exact level of sedation reached is determined by patient characteristics and drug dosage.

Younger children may require deeper sedation to reduce agitation, although, except in infants, the metabolism of sedatives is not dissimilar in children and adults [3, 10]. Nonetheless, deep sedation may be more of a problem in children than in adults [5]. In children—given their smaller size, increased compliance, and the prominence of the tongue within the oral cavity—airway resistance is greater. With manipulation of the upper airway, infants are prone to apnea. Older children may have tonsillar or adenoidal hypertrophy. Furthermore children with EA also have poor esophageal clearance.

In children and adults, conscious sedation involves a combination of a benzodiazepine and an opioid [5, 17]. Administration is titrated, allowing time between doses to assess the response. The current practice in the United States, most often, is to use a combination of midazolam (in boluses of 0.1–0.2 mg/kg body weight) and fentanyl (1–3 μg/kg body weight) [5, 18]. Both of those drugs have a short duration of action. The dose-dependent respiratory depressive effect of a benzodiazepine is exacerbated by simultaneous administration of an opioid [19].

For pediatric endoscopy, propofol (a sedative hypnotic) is being used with greater frequency [5]. It has a very short half-life and therefore the potential for rapid onset of, and rapid recovery from, sedation [20]. With propofol, the level of sedation can be controlled for a prolonged period. But because of its narrow therapeutic range, it has a propensity to cause deep sedation; at most centers, administration and monitoring must involve an intensivist or anesthesiologist [5, 21, 22]. In smaller children, recovery after sedation with propofol may be prolonged. Ketamine is also used as a single agent and is preferred at some centers. However, significant contraindications to its use [5] and an associated risk of laryngospasm make it less suitable for upper endoscopy, especially in younger children [23, 24].

Subjecting small children to general anesthesia for endoscopy is based on the perception that they will not tolerate sedation. It is agreed that complex prolonged procedures should be performed under general anesthesia, especially if they increase the risk of pulmonary aspiration [10, 25–28]. One prospective study of 226 endoscopic procedures, comparing conscious sedation with general anesthesia, found that the comparative completion rate with conscious sedation was 95 % [19]. Another prospective study of conscious sedation for upper endoscopy in children, including a significant number of high-risk patients, found that all 34 procedures were completed [29]. Similarly, a retrospective study of over 600 outpatient procedures found that the completion rate with conscious sedation was more than 99 % [30]. Regarding safety, one prospective study of 36 children under 6 years of age found that a significantly greater number of oxygen desaturation episodes occurred in sedated children than in those who underwent general anesthesia; in addition, operator satisfaction was better with general anesthesia [31]. A prospective study of capnography during sedated endoscopic procedures documented poor ventilation during 3 % of the procedures, alveolar hypoventilation during 56 %, and apnea during 24 % [25]. It is understandable that exclusive use of general anesthesia for all endoscopies may be increasing, especially in younger children [21]. The argument against general anesthesia includes the possibility of mechanical injury during endoscopy, because of excessive force in a patient who is unable to respond. Mucosal damage can be significant, but reports of upper and lower endoscopic perforation are rare [18, 32].

There is no data comparing sedation and anesthesia specifically in EA patients. General anesthesia is not necessary for endoscopy in adults with a remote history of EA. At our institution, in small children with EA, we have always used general endotracheal anesthesia for any endoscopic procedure.

Long-gap EA patients at our institution have mostly been referred from outside centers and have had the most challenging histories. Typically, those EA patients were not able to undergo a primary repair or underwent one or more failed attempts at repair elsewhere. Such attempts may have led to an esophageal fistula to the hemithorax, compromising lung function and leading to chronic empyema. Also common in

referred long-gap EA patients has been a history of recurrent pneumonia (associated with prolonged drainage of the upper esophageal pouch) or the presence of an esophagostomy, not uncommonly tracheal stenosis (from repeated or prolonged intubations), tracheomalacia, bronchomalacia, or the presence of a tracheostomy. Clearly in this patient group, it is imperative to control the airway during any sedated procedure, and anesthesia is the preferred method for endoscopic procedures.

Equipment and Technique

Developments in endoscopic equipment and techniques have been well described in most relevant textbooks and, especially in children, have been updated periodically [10, 33, 34]. In adults, larger-caliber upper endoscopes have better optics and more channels for instruments; in children and in nonsedated adults, smaller-diameter scopes more easily facilitate procedures. Standard adult gastroscopes (>8.7 mm in diameter) are also used in older children (weighing 10 kg or more); smaller instruments (5–8 mm in diameter) are available for gastroscopy in infants. Scopes of 5–6 mm in diameter can be used in infants as small as 2.5 kg. I have accessed gastrostomy sites using adult bronchoscopes; however, visibility, maneuverability, and instrumentation are limited.

The principles of upper endoscopy with or without therapeutic intervention are the same in children and in adults. Because of the limited data in children, guidelines for them are mostly extrapolated from adult data [10]. The smallest instruments (5–8 mm in diameter) have smaller channels (2.0 mm) than standard gastroscopes (2.8 mm in diameter). Specifically, catheters of 7 French (7F) and greater cannot be inserted, limiting the use of electrocautery.

No studies in small children have been published that would help define the choice of injectable agents and doses, heater probes, monopolar and bipolar cautery, or specific devices and settings. However, case reports have described most techniques used in adults [3, 10], and detailed reviews of methods used in children have been published [34]. Operator decisions depend on training, experience, and preference, with safety kept in mind at all times [10]. For upper endoscopy at our institution, we typically use a scope with a channel of 2.8 mm in diameter in patients who weigh at least 10 kg [35]. We have previously showed that argon plasma coagulation can be performed through smaller endoscopes using a small probe (1.5 mm in diameter) [35, 36]. Intubation of the esophagus is not of special concern as compared to other infants though if stenosis is suspected such as at the anastomotic site, a small-caliber endoscope is ideal for the initial examination.

Monitoring

During sedated adult and pediatric procedures, including endoscopy, the use of pulse oximetry and hemodynamic monitoring is routine. In the case of infants regardless of whether they have EA, we have found it essential to use anesthesia either in the operating room or in the pediatric intensive care unit with propofol, in order to optimize monitoring and support [10, 35–38].

During sedated procedures, a nurse trained in pediatric life support should monitor vital signs throughout the procedure [5]. Oxygen administration has been advocated: data suggest that a significant proportion of children develop oxygen desaturation and/or arrhythmias during conscious sedation for endoscopy [25, 31]. In deeply sedated patients, hypoventilation may be a significant issue that is potentially masked by oxygen administration [25]. In children, their greater surface-to-volume ratio and thinner skin predispose them to hypothermia and to fluid depletion. Endoscopic procedures are usually brief, but those involving therapy may be prolonged, so children should be well draped. Additionally, room temperatures will need to be controlled to avoid hypothermia. Similarly, fluid balance should be managed scrupulously. Monitoring should continue throughout the recovery period, until the patient shows spontaneous activity and maintains cardiovascular reflexes.

The principles of monitoring are not different in EA patients, whether infants or older. For intubated procedures, especially in very young patients, careful monitoring should include vigilance for potential dislodgement of the endotracheal tube. Infants, whose trachea may be only 2–3 cm long, are intubated with uncuffed endotracheal tubes, making dislodgement of the tube very possible during withdrawal of the endoscope.

Complications

Complications are uncommon during routine endoscopy in adults and children [38, 39]. Methemoglobinemia from the use of topical benzocaine is periodically reported [40]. In sedated patients, transient hypoxemia and arrhythmia can occur. Persistent hypoxemia and hypoventilation should prompt removal of the endoscope and physical assessment. In patients who have respiratory difficulty during or after the procedure, pulmonic aspiration should be considered.

Complications that begin beyond the immediate post-procedure period are less significant. In a survey of 393 pediatric patients 30 days after upper endoscopy, 42 % noted one or more symptom, the most common being a sore throat; 6 % sought medical advice for their symptoms, but none had a serious complication [41]. In a similar study of surveys taken after upper and lower endoscopy, symptoms were reported in 15 % of children [42].

As mentioned, bacteremia is unusual after routine endoscopy. In otherwise healthy children who have undergone endoscopy limited to the esophagus, traumatic perforation and bleeding as a result of mildly abnormal coagulation studies are rare [43].

There is little data specifically addressing complications of endoscopy in EA patients, and it is reasonable to assume that complications reported in non-EA patients can occur equally frequently in EA patients. As noted above, the potential for accidental extubation is significant in small children, especially during therapeutic procedures or with prolonged manipulation of the endoscope. In our patient population, we place devices such as high-resolution endoscopic ultrasound (EUS) probes and dilating balloons alongside the endoscope in small children. Doing so adds to the degree of complexity and to the possibility of complications.

Patients with Esophageal Atresia (EA)

The most common symptoms in EA patients are a combination of dysphagia, food impaction, heartburn, regurgitation, and respiratory symptoms. The pathophysiology of upper GI problems in EA patients is related to esophageal dysmotility, an inability to clear the lower esophagus, a reduced lower esophageal sphincter (LES) tone, and the absence of a normal reflex opening of the LES, the potential for a hiatal hernia, and narrowing of the anastomosis.

Long-Gap EA

At the University of Minnesota program for long-gap EA repair, the initial workup of patients includes endoscopy as well as contrast imaging. Again, our patients are typically outside referrals for primary repair with traction, so they often have an upper pouch that is constantly drained by an oral tube under some degree of suction. It is important at this stage to know the integrity of the most distal portion of the pouch before traction and to examine the effect of constant suction on mucosal integrity. Of critical importance is the presence of an upper pouch fistula; at our institution, we have located upper pouch fistulas that had not been identified in previous investigations.

Similarly, any lower pouch fistula must be identified and some impression of lower pouch integrity obtained before traction.

Details of the surgical technique for long-gap EA repair at our institution have been published elsewhere [2]. In brief, to estimate the esophageal gap, we use radiologic studies before surgery and confirm the results intraoperatively. During the initial operation (a posterior right thoracotomy

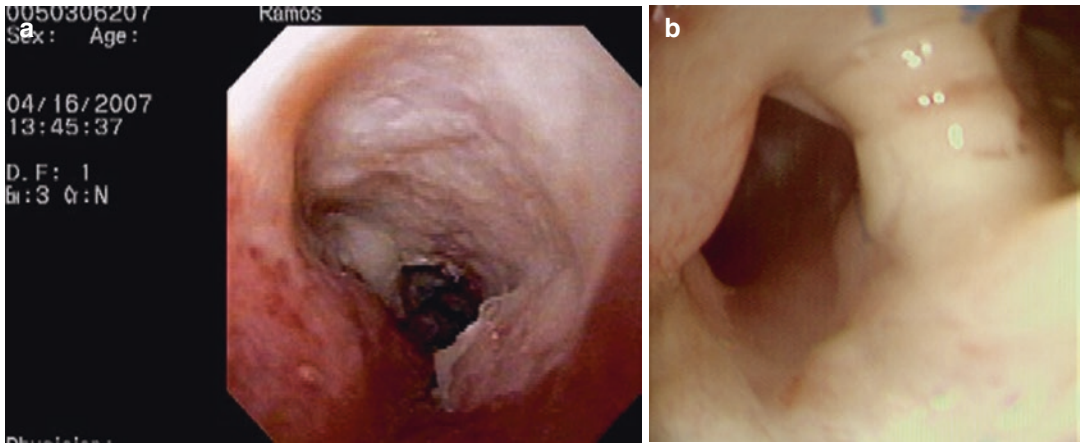

Fig. 34.1 (**a**) Extensive granulation at the site of an anastomosis signifying an underlying mural defect. (**b**) A large fistula at the site of an esophageal atresia repair

between the fourth and seventh ribs), the two ends of the esophagus are dissected and the possibility of a primary anastomosis assessed. If such an anastomosis is not possible even under tension, pledgeted traction sutures (5.0 Prolene horizontal mattress sutures) are placed in the esophageal ends and then traction applied. For external traction, the sutures are brought out of the back, above, and below the incision and tied over Silastic buttons. Between one and three times per day, the sutures are shortened to maintain tension until the two ends of the esophagus are 1 cm apart (per radiologic assessment of clips applied near the ends of the esophageal pouches).

The role of endoscopy during placement of traction, and then intermittently during maintenance of traction, includes examination for leaks. At our institution, we have also found it important to compare lumen depth (as gauged by endoscopy) with the position of the radiopaque markers that distinguish the position of the traction sutures; doing so helps determine whether the sutures have slipped and therefore need to be replaced. The clearest indication of slippage is a large gap between the end of the scope marking the most distal position of the lumen and the sutures. Further evidence of slippage is advancement of sutures while lumen depth remains the same.

During placement of traction sutures, simultaneous endoscopy can facilitate examination of the distal portion of the pouch for integrity. It can also help identify the distal end, a task that may be difficult in patients who have undergone multiple operative procedures with resulting scarring. We have used direct vision for placement of rubber tubing, in order to intraoperatively align the two pouches in patients whose distal pouch lumen is small and narrowed.

Anastomosis

In typical EATEF patients, the ends of the upper and lower pouch are not difficult to bring together, so a primary repair is performed soon after birth. In such patients, endoscopy is not necessary either before or after the surgery. An assessment of the anastomosis may be necessary only to determine the cause of upper GI symptoms. Our long-gap EA repairs are only possible with significant tension during the anastomosis. This likely increases the possibility of a leak at the anastomosis and of eventual stricture formation. To explore for leaks, we have therefore used a combination of endoscopy and water-soluble contrast. Radiologically, a leak may be missed if there is a great deal of granulation tissue at the anastomosis (Fig. 34.1).

The anastomosis is examined endoscopically most often to determine the presence of narrowing that needs to be dilated and for the presence

of inflammation, which suggests acid reflux as part of the pathophysiology for stricture formation. Diverticula though rare do occur after EA repair and may be a cause of symptoms. In our patients, endoscopy and EUS (see below) have been used together to examine diverticula muscular integrity and estimate the length of the stricture in patients with recurrent stricturing; diverticula devoid of muscle tissue may benefit from excision, and a long stricture may benefit from surgical revision, rather than persisting with dilation.

Lower Esophageal Sphincter (LES)

To ascertain dysfunction of the LES, endoscopic assessment is an important adjuvant to manometry and radiologic studies. The most critical findings are the location of the Z-line and differentiation between a true Z-line and gastric or intestinal metaplasia (see next section). A patulous LES is an obvious sign of dysfunction; combined with a finding of Z-line migration caudally, it can be good evidence of a hiatal hernia and therefore the need to relocate the LES in the abdomen. In some patients, the LES may be tight following fundoplication; resistance to passage of the endoscope can indicate that the LES needs dilation. The lower esophagus otherwise lacks propulsive motility and the normal relaxation reflex of the LES. The degree of dysfunction of the LES after a fundoplication can also be gauged by examination of the fold that appears in the fundus of the stomach. Loosening of the fundoplication is characterized reduction of these folds.

Dysphagia and Endoscopic Findings

Patients with a history of EA repair most commonly suffer from dysphagia and food sticking in the chest. The diagnostic possibilities include a narrowed or stenotic anastomotic area, a tight LES, and extrinsic compression from a narrowed diaphragmatic hiatus. Even in the absence of an obstruction, the lower esophagus is devoid of propagating contractions, and the LES does not open in the normal manner to allow progression of a swallowed food bolus. Therefore, depending on the characteristics of the bolus, dysphagia may occur in most EA patients, even those with no complaints [44].

Reflux of gastric contents can also cause the same symptoms, only rarely are defects, such as shelves and diverticula, from the repair process to blame. Data specifically on EA patients are lacking, but in older children and adults, meat is the most common source of impaction [45, 46]. In otherwise healthy people without a history of EA, investigations of dysphagia are imperative; in EA patients, the value of such investigations needs to be balanced with what is already known about the patient since likely a degree of dysphagia is related to esophageal dysmotility. If food impaction does not resolve on its own and if noninvasive maneuvers have failed to relieve symptoms or there is suspicion of a foreign body, then endoscopy is indicated. All esophageal foreign bodies should be removed promptly, in order to prevent esophageal ulceration, perforation, and possible aortoesophageal fistula. One survey found a success rate of almost 99 % for removal of foreign bodies from the upper GI tract in children, with no significant complications [47]. Techniques for dealing with food impaction and for removal of foreign bodies involve a combination of snares, forceps, and overtubes. The exact method will depend on the nature of the foreign body, its location, and the preference of the endoscopist. Food can be advanced into the stomach using the scope itself, without the need to attempt removal. Endoscopic examination at the time can help assess additional reasons for dysphagia (Fig. 34.2).

In difficult cases, we have used a dilating balloon inflated to low pressures with contrast, examining the passage of the balloon through the anastomosis and LES for any subtle evidence of obstruction. We would also advocate obtaining a biopsy sample from the lower esophagus and anastomosis, in order to further elucidate the cause of the impaction. Eosinophilic esophagitis should also be considered in patients with new-onset dysphagia; it is increasingly reported in the general population of adults and children and

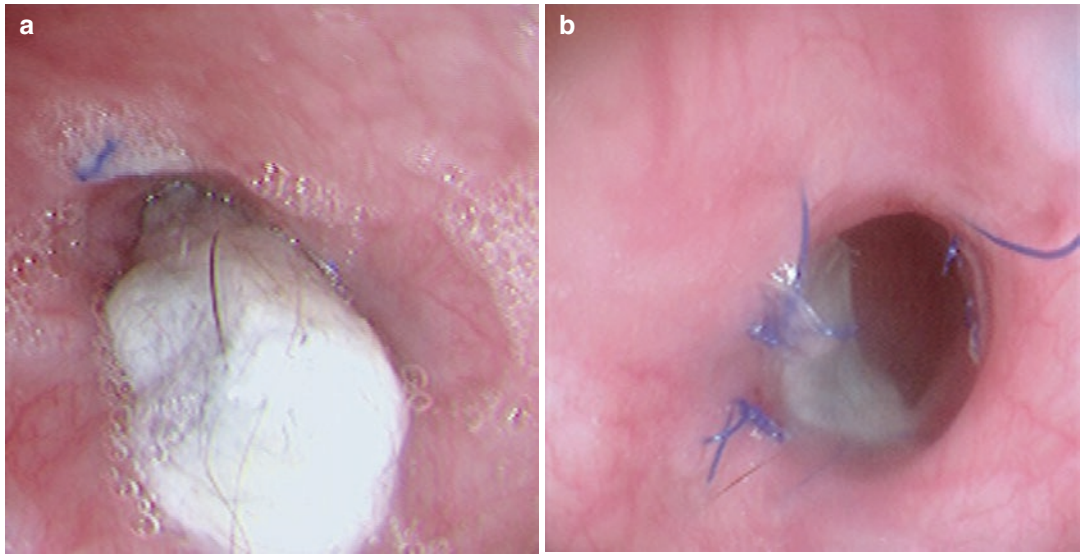

Fig. 34.2 (**a**) Findings in an infant who stopped feeding. (**b**) After removal of the cotton ball seen in **a**, the anastomosis was also dilated

typically presents as dysphagia. In our series of more than 70 patients with long-gap EA, 1 had eosinophilic esophagitis on long-term follow-up.

Esophagitis and Barrett's Metaplasia

As noted above, the lower esophagus after EA repair is dysmotile, and the LES does not normally relax to allow swallowing. Esophageal inflammation can therefore result from food bolus contact for prolonged periods, possibly complicated by pH changes. Such changes not only will cause erosions but may also give false-positive information on acid reflux. Still, the main concern outside of anastomotic problems is that of GER [44, 45, 48–53]. Most published data on endoscopy in EA patients is retrospective, and most available data is based only a proportion of patients surveyed and those consenting to procedures [49].

Data from long-term studies that have reported endoscopic findings make it clear that the prevalence of serious sequela (such as Barrett's esophagus) may be significant and that routine surveillance endoscopy should be the norm [44, 45, 48–53]. A long-term follow-up study of 23 patients who agreed to undergo EGD found that macroscopic Barrett's esophagus was diagnosed (and confirmed by histologic analysis) in one patient. A second patient developed squamous cell esophageal carcinoma [54]. A study of 62 patients who were at least 20 years old (identified from a database and invited to undergo a clinical endoscopy) found reflux esophagitis in 36, Barrett's esophagus in 7, and strictures in 26 [49]. And one patient had esophageal squamous cell carcinoma. Men who were at least 35 years old and patients with severe reflux symptoms were at high risk of having severe esophagitis or Barrett's metaplasia. One study of 49 patients 10 years after EA repair for EGD found severe esophagitis in 2 and macroscopic Barrett's esophagus in 2 [55]. Histologic analysis found esophagitis in 30 patients, gastric metaplasia in 3, and no intestinal metaplasia. Investigators surveying EA patients of whom a proportion consented and then underwent endoscopy have shown similar findings [44, 45, 48, 49]. Tovar et al. found, through histologic analysis, esophageal inflammation in 51 % and Barrett's esophagus in 6 % of their series of patients [50].

The difficulty with interpreting these long-term studies is often the degree of inflammation

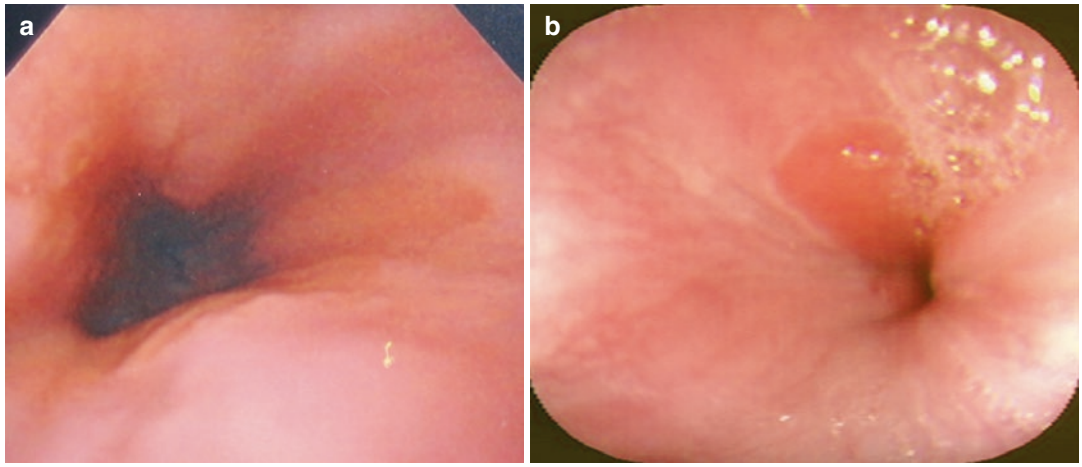

Fig. 34.3 (**a**) The appearance of the lower esophagus in a patient with a history of esophageal atresia repair suggestive of Barrett's metaplasia. Mucosal histology was consistent with gastric cardia-type mucosa. (**b**) A lip of abnormal mucosa in the lower esophagus that was confirmed to be gastric metaplasia

per histologic analysis and the rarity of histologically confirmed Barrett's esophagus. Most patients in such studies may have cardiac-like gastric metaplasia or movement of the Z-line upward as part of a hiatal hernia. In our group of long-gap EA patients, some abnormal mucosa to suggest was seen in 3 of over 70 children on follow-up endoscopy (Fig. 34.3). Histology showed mucosa characteristic of gastric cardia. Yet findings of inflammation of the lower esophagus are highly significant, mandating long-term follow-up. The precise schedule is unlikely to be decided by available data, so is at the discretion of the gastroenterologist familiar with EA patients. And while histologic Barrett's esophagus in children with EA is rare in such patients, we highly recommend regular endoscopy and appropriate treatment of any inflammation.

Endoscopic Ultrasound (EUS)

EUS is extensively used in the investigation of adult-onset GI pathology. It is a particularly useful diagnostic tool for hepatobiliary and pancreatic disorders. In the esophagogastric area, the typical indication for EUS in adults is to examine structures beyond the esophageal wall of the intestinal lumen. High-resolution EUS has limited depth but provides great detail (as compared with standard EUS). It is therefore ideal for studying the GI mural structure but has limited effectiveness for imaging structures beyond the esophageal wall. Perhaps as a result, it is not routinely used for any specific indication in adults but has been used to investigate esophagitis as well as esophageal and esophagogastric muscle contraction and motility [56–59].

Few reports have documented the use of high-resolution EUS for esophageal disorders in children [60–62]. Fox et al. [62] examined the esophagus in children with eosinophilic esophagitis and found an expansion of the mucosa and submucosa (as compared with controls).

Our practice of employing high-resolution EUS in EA patients dates back several years [63–65]. All EUS procedures are performed during EGD and under anesthesia, using a 20-MHz catheter ultrasound probe (2.4 mm in diameter) (UM-3R, Olympus America, Inc., Melville, NY) and an ultrasound processor (EU-30, Olympus). We have used standard endoscopes with a channel for infusion of water separate from the standard accessory channel (for the EUS probe), except in infants (<10 kg), in whom the EUS probe is passed alongside a smaller endoscope. Sterilized water (5–20 cc) is infused into the esophageal lumen for acoustic coupling (total of

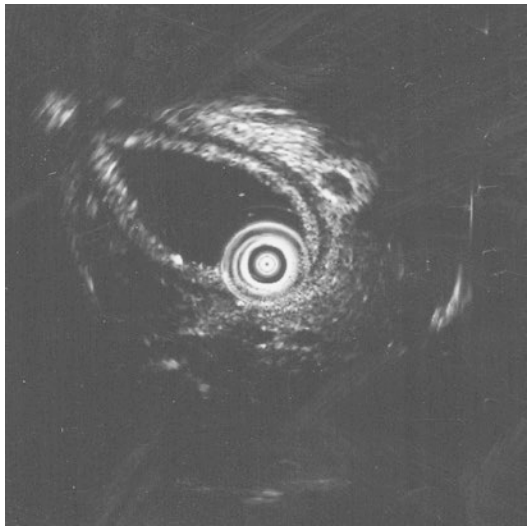

Fig. 34.4 The mural structure of the esophagus; the muscularis propria is most easily seen as a hypoechoic area

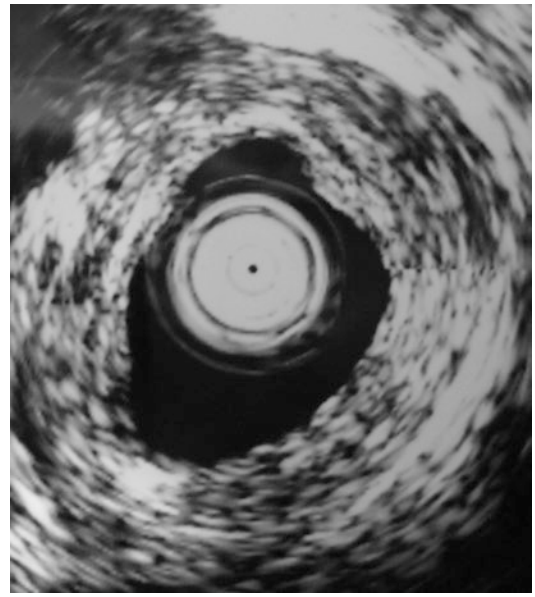

Fig. 34.5 The typical appearance of a fibrotic anastomosis on endoscopic ultrasound

100–120 cc). We used the method to assess the effect of traction on the mural structure of the esophagus. The main aim was to examine whether there is a simple stretch of the esophagus or actual growth of tissue when the esophagus elongates under traction. Ultrasound images were examined to establish anatomic layers as previously described [66]. The innermost hyperechoic layer corresponded to the echo interface and the adjacent hypoechoic layer to the mucosa; the third hyperechoic layer, to the submucosa; the fourth hypoechoic layer, to the circular smooth muscle layer; the fifth hyperechoic layer, to the interface between muscle layers; the sixth hypoechoic layer, to the longitudinal smooth muscle layer (muscularis propria) (Fig. 34.4); and the seventh, outermost, hyperechoic layer, to the adventitia.

In our study, we found that the depth of the mucosa and submucosa in patients with EA was 0.99–1.10 mm—similar to the depth previously reported in healthy control patients [64]. We interpreted this as good evidence supporting our hypothesis that mural growth under tension allows primary repair to be performed. Furthermore there was no significant change before and after repair of both the upper and lower segments [65]. In other case reports, high-resolution EUS has been used to determine the nature of esophageal stenosis before resection, differentiating cartilaginous from fibrotic strictures (Fig. 34.5) [60, 61]. Of potential relevance to EA patients, Kamijo et al. [67] showed that prognostic information could be obtained on stricture formation in the days after ingestion of corrosives. Similar to the experience of others [62], we were unable to always discriminate the intermuscular layer, mucosa, and submucosa as separate layers with the 20-MHz probe (Fig. 34.4). With high-frequency probes, others have occasionally found a nine-layer structure of the esophageal wall in which the mucosa, muscularis mucosa, and submucosa appear as separate layers [68].

We found that the high-frequency catheter EUS probe was easy to apply for examination of the esophagus in children with EA, although the need to infuse water for acoustic coupling was a limitation. That need was reported to be a particular problem when attempting to examine the upper esophagus in sedated children [62]. We would add that infusing water in the upper esophagus is also a risk for aspiration and that the airway should be protected especially in EA patients where there is

esophageal dysmotility. Other investigators have found infusion of ultrasonographic jelly to be effective for acoustic coupling [67].

Despite these shortfalls, we propose a number of further uses for high-resolution EUS in children with EA: when it is difficult to decide, perioperatively, on traction in very small distal segments; when stricture length needs to be assessed for the purpose of accurate resection; when the potential for formation of diverticula needs to be predicted after myotomy [69]; and potentially when esophageal motility needs to be examined in the proximal segment after traction, in order to predict esophageal function [59].

Summary

In the EA population, we have found upper endoscopy to be highly useful as part of the early management of difficult cases, and it is clear that long-term endoscopic surveillance of patients should be a routine part of their follow-up. We have added high-resolution EUS for critical assessment of the mural structure of the esophagus when using traction as part of the management of long-gap EA patients, and this modality may have other potential uses in this patient population.

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Complications Following Pediatric Esophageal Surgery

35

Sigmund H. Ein

Complications Following Esophageal Atresia Repair

Philosophy and Reality of Esophageal Atresia Repair

The old teaching that the original esophagus, albeit not properly formed, is infinitely better (after its repair) than any substitute still exists. In 1965, Howard and Myers stated: "It is our firm conviction that the best esophagus possible is one which is constructed entirely from the elements originally developed for its formation" [46]. However, trying to repair the baby's original esophagus must not compromise the baby's life. Therein is the art, as well as the science, of pediatric surgery, and experience plays a huge part in both of these areas.

If pediatric surgeons do enough esophageal atresia (EA) surgery, they will have their share of complications! Nonetheless, they must minimize their occurrence and deal with them accordingly.

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Anastomotic Leak

This is by far the most worrisome complication of an EA repair and classically occurs on the third or fourth postoperative day; many are relatively asymptomatic and therefore go clinically unnoticed. The clinical manifestations depend upon the size of the leak, but, surprisingly, there does not seem to be any correlation between the tight, difficult anastomosis and the incidence of anastomotic leak. The reported incidence of leak varies from 4 to 40 % with a higher leak rate in the far less commonly done end-to-side Duhamel anastomosis [17, 28, 39, 63, 82]; the two-layer anastomosis is reported to have a lower leak rate (and a higher stricture rate) but is not done as often as the single-layer anastomosis [17].

If the anastomosis virtually falls apart, the signs and symptoms of respiratory distress suddenly appear in an acute fashion, earlier than usual, on the second or third day. At the other end of the spectrum, the only evidence of a tiny asymptomatic leak may be the radiological finding of a bit of extravasated water-soluble contrast at the sight of the anastomosis, usually when the first routine contrast swallow is done at the end of a week. The baby can continue to feed via an intraoperatively placed nasogastric feeding tube [3] (or gastrostomy tube), and the contrast study should be repeated at weekly intervals until the leak disappears, usually in a week or so [33]. This leak would probably disappear even if the baby was allowed to feed per os on the day it was discovered; however, it is best not to allow the

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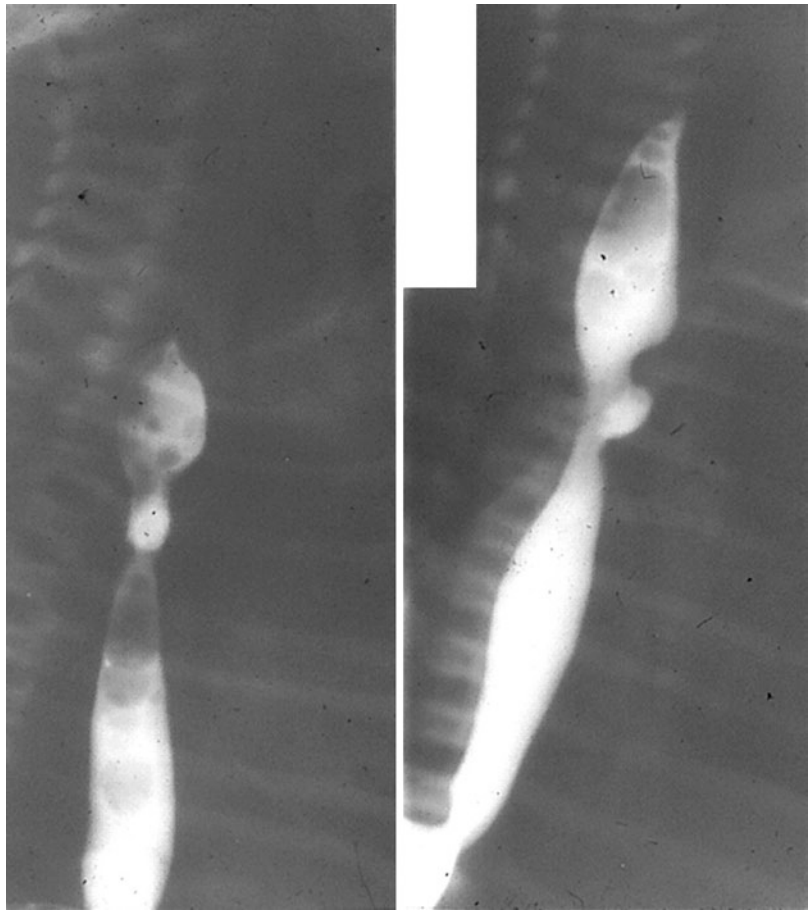

Fig. 35.1 Anastomotic diverticulum after EA repair

baby to feed by mouth to avoid an anastomotic diverticulum (Fig. 35.1) from developing, let alone a recurrent tracheoesophageal fistula (TEF). There have been as many esophageal anastomoses leak without a transanastomotic feeding tube as with one [33].

The typical anastomotic leak presents with some acute respiratory distress; the baby becomes cyanosed, tachypneic, gray, and septic. A chest x-ray usually shows the almost typical right pneumothorax (Fig. 35.2) or pyopneumothorax which is sometimes captured by the indwelling chest tube (Fig. 35.3). If the original chest tube, placed at the operation, does not work because it is plugged (more often than not), then a second one will have to be placed (nowadays, often by interventional radiology (IR) to be certain it adequately captures and drains the leak). It is for this reason that a chest tube is often not left at the time of repair [8]; there is nothing that upsets parents more than a second and a third chest tube.

The respiratory distress necessitates the following emergency measures: the upright positioning, the halting of feedings (oral and/or tube), and the administration of oxygen and antibiotics. If the respiratory distress is severe and/or the baby tires, he/she should be intubated and put on a ventilator for a few days until the emergency is over and his/her condition is improved. One or both chest tubes will almost certainly drain some saliva, and only when this stops does it usually mean that the leak has closed. It is at this time that a water-soluble contrast esophagus examination is carried out to assess the anastomotic leak (Fig. 35.4). Usually, the later the leak occurs, the smaller it is and the less severe the

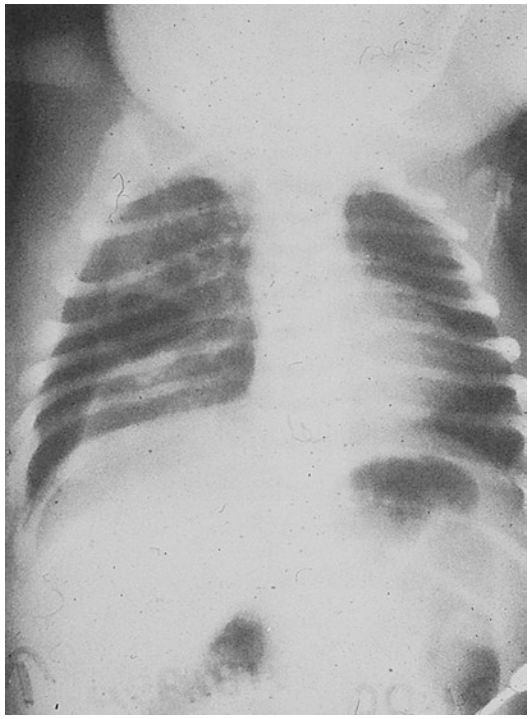

Fig. 35.2 Chest x-ray showing typical right pneumothorax because of leaking EA anastomosis

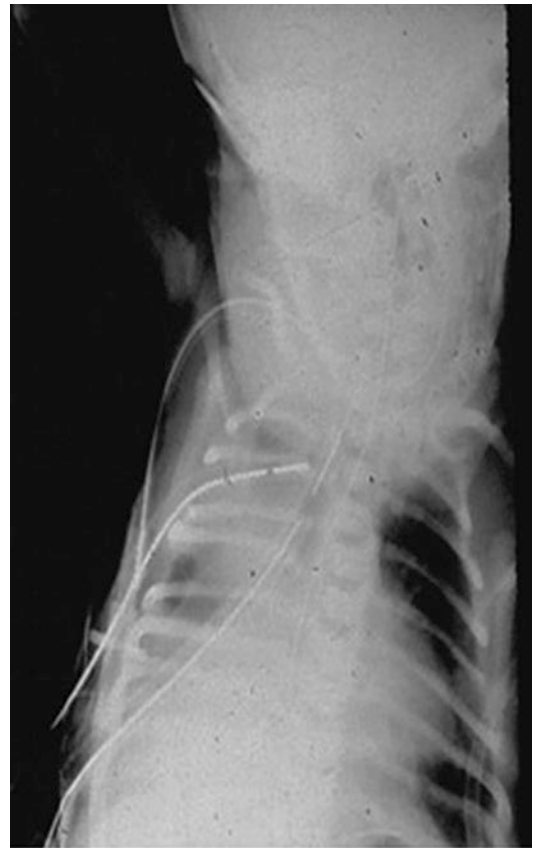

Fig. 35.3 Chest x-ray showing common pyopneumothorax, which is sometimes captured by the postoperative chest tube

clinical picture. When it has healed, the baby can feed by mouth. There is never any reason to get a contrast swallow as soon as the leak occurs, because the baby is often too sick for the study and besides, it should not influence the above treatment in any way. Moreover, there is never any indication for reoperation on a leaking anastomosis, because repair in the presence of inflammatory tissue is rarely successful and leads to total disruption of the two pieces of esophagus, which of course commits the baby to an immediate esophagostomy in the neck and later an esophageal replacement. It is amazing, but true, that these leaks all heal in time, albeit usually with some degree of stricture.

The chest tube(s) usually is not removed until the leak has closed; this may take several weeks and occasionally the chest tube slips out on its own. If this happens, it invariably means that it does not need to be there any longer because the pleural cavity has sealed itself around the tube. Sometimes after the tube is removed, all that remains is an esophagocutaneous fistula, which is occasionally perpetuated by the tube; that too will close in days, during which time oral feeds can restart. One of the supposed advantages of the retropleural (extrapleural) approach for the repair of EA is that this procedure minimizes the effects of such a leak by not soiling the pleural cavity and lungs; however, the babies are just as sick [38]. It is surprising how well the right chest improves as healing occurs over the next number of weeks.

Stricture and Gastroesophageal Reflux

The majority of babies who have undergone repair of EA do quite well and go home feeding normally within a few weeks after surgery. It is extremely rare to view a postoperative contrast swallow and not see the anastomosis; it is always somewhat narrowed (Fig. 35.5). If the neonate feeds well during the first few weeks and months,

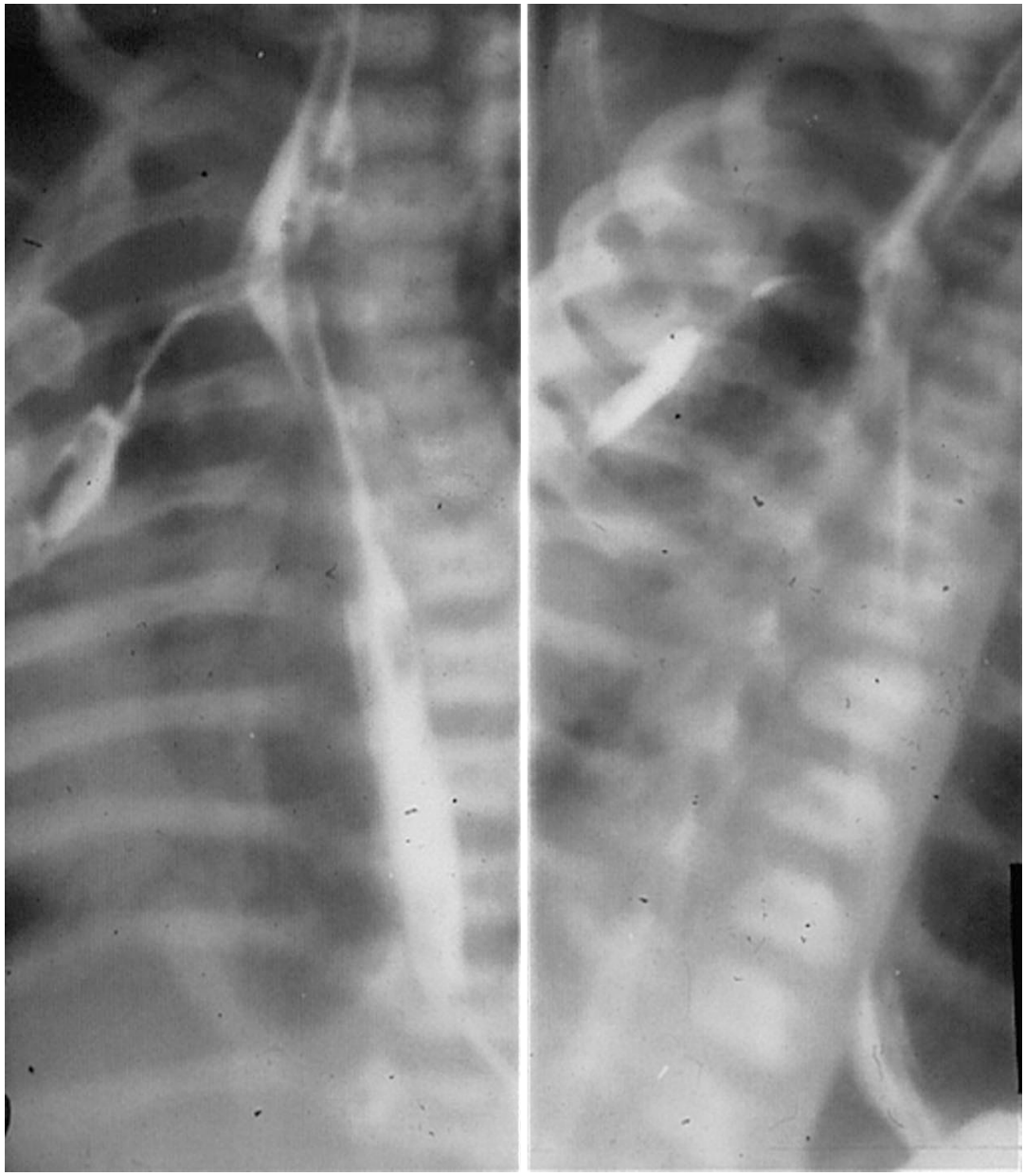

Fig. 35.4 Water-soluble contrast (safer than barium, which may remain outside of the lumen forever) esophagram examination to assess anastomotic leak

and even if the x-ray shows a fairly tight anastomosis, it is reasonable to just follow him/her; the patient should be treated and not the x-ray. The rationale of routine postoperative esophagoscopy after every esophageal repair does not seem warranted and is not done by many pediatric surgeons; moreover, most narrowings will improve on their own in time (Fig. 35.6). An important point to remember, when evaluating a postoperative contrast esophagram, is not to check how narrow the anastomosis looks, but to see how wide it can open. Some series report strictures requiring dilatation in as many as 80 % of EA patients [39]; this seems high.

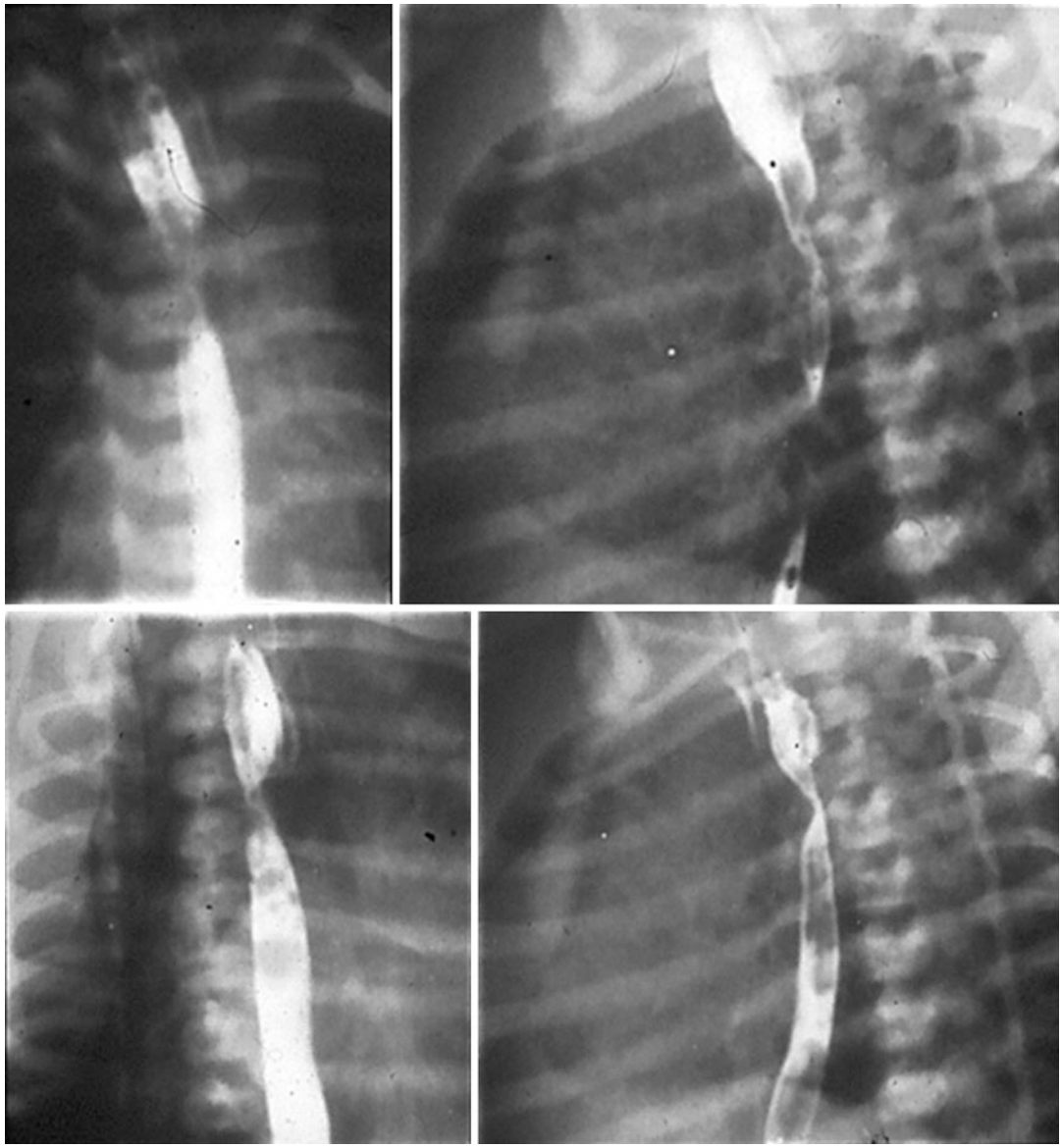

Fig. 35.5 Postoperative (PO) contrast esophagram (usually done on PO # 7) to assess EA anastomosis. It is extremely rare to not see the anastomosis, which is always somewhat narrowed

Stricturing at the site of anastomosis may progress quite far, before the infant on a fluid diet presents with coughing spells, aspiration, regurgitation, and failure to gain weight (Fig. 35.7). That is the time for a water-soluble contrast swallow (esophagram) to confirm the stricture. Most, if not all, strictures respond to dilatation, which can almost always be carried out prograde and without the use of a gastrostomy and stringing. There are several ways to go about these dilations: bougies blindly in the clinic; direct vision esophagoscopy in the operating room under general anesthesia; balloon dilators in the interventional suite; and Tucker bougies prograde or retrograde using a Marlex string as a guide wire coming out the gastrostomy.

Dilatations can be done on a routine planned basis (even if asymptomatic) or on demand (if

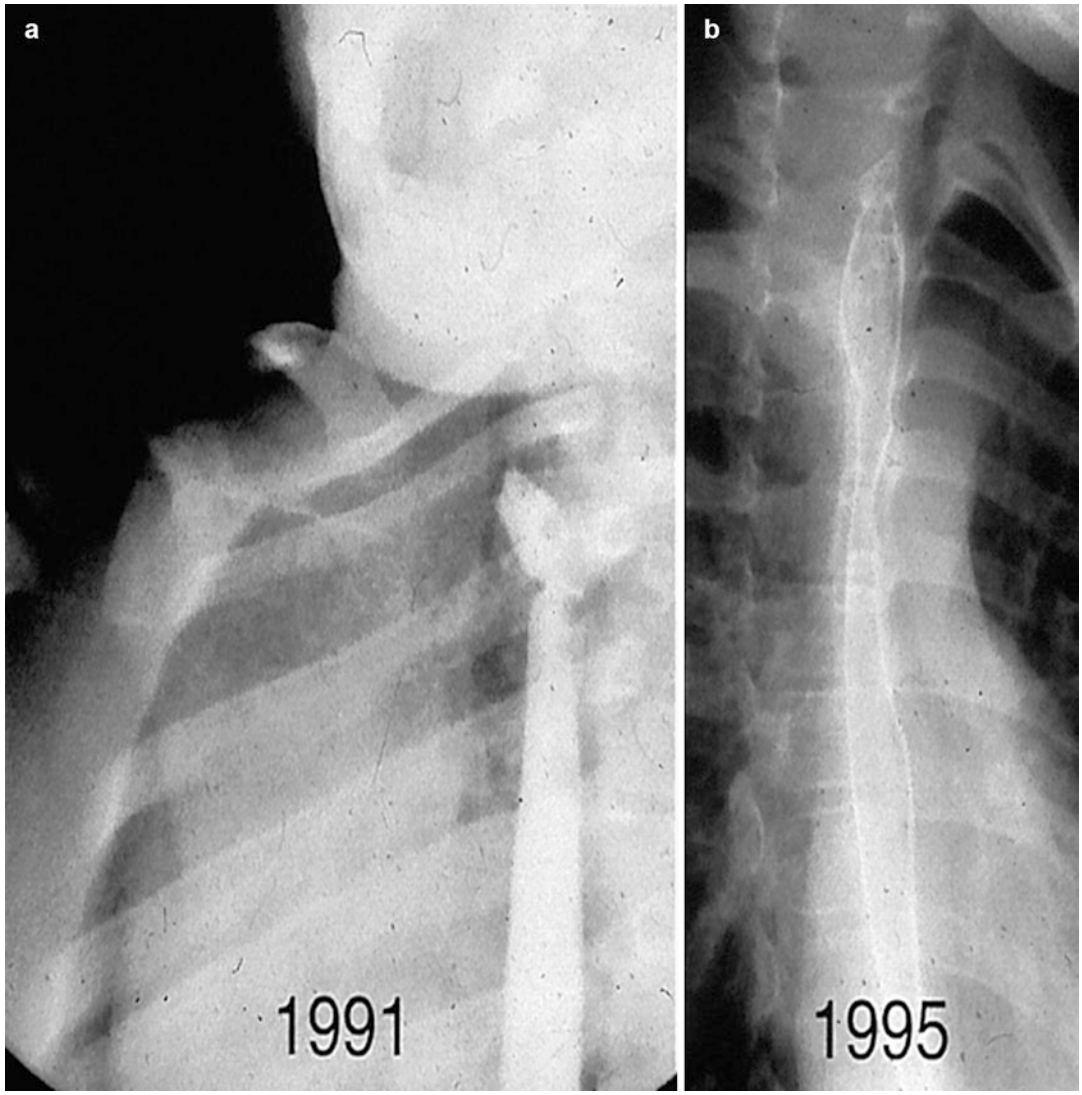

Fig. 35.6 Contrast esophagram of same repaired EA patient at age 1 year (**a**) showing asymptomatic anastomotic narrowing and (**b**) 4 years later a marked improvement without dilatation

symptomatic). Initially, dilatation of the short, tight strictures may have to be carried out weekly, but after a few such procedures, an obvious decrease in symptoms and increase in lumen size should be apparent. The interval between dilatations may then be extended on an individual basis. Many strictures respond to one to three dilations [39]. Should the stricture fail to respond to dilatation, or the response is transient, one must rule out gastroesophageal reflux (GER) (Fig. 35.8). It has been stated that about 80 % of EA babies reflux, but only 20 % of them are symptomatic, in that they require treatment [60]. Therefore, in such symptomatic situations, if the latter problem is not corrected medically or surgically, little permanent response to dilatation can be expected [62]. The drawback to an antireflux procedure is that because of the poor distal esophageal peristalsis in all babies with EA, they cannot be snugged up too tightly; otherwise, they will be obstructed and worse off than before. Therefore, of necessity, the recurrence rate of antireflux procedures in these

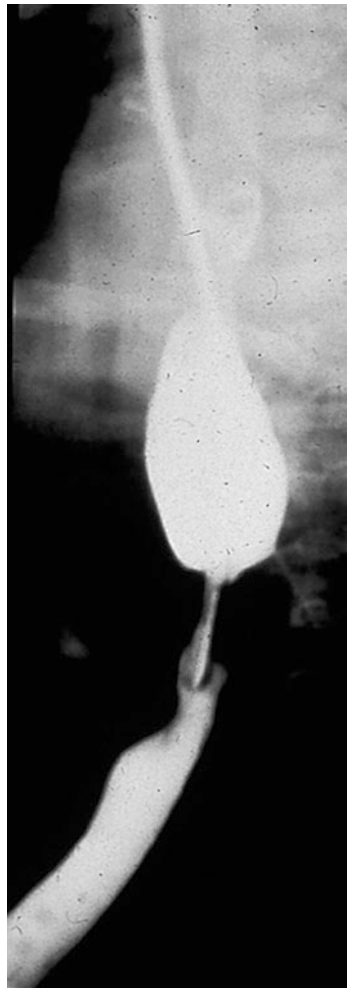

Fig. 35.7 Marked EA postoperative anastomotic stricture which has progressed quite far without symptoms because the infant is only on a fluid diet

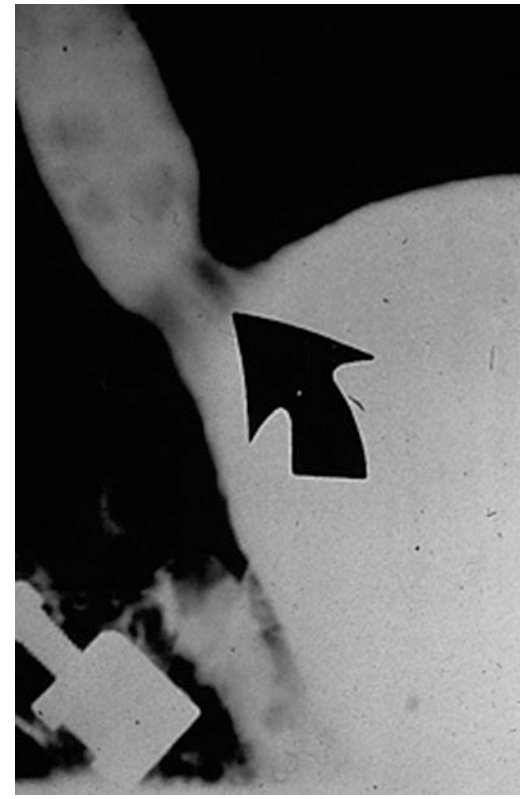

Fig. 35.8 Marked GER (*arrow*) perpetuates a postoperative EA anastomotic stricture which has failed to respond to dilatations

infants is high (about 30%). Fortunately, aggressive medical treatment seems to be adequate in most cases. The same applies to the occasional distal esophageal narrowing (either congenital or acquired – GER).

It is unusual that dilatation is required beyond a year or 2 of age, and it is rare to have to resect a strictured anastomosis. Even when the anastomosis is virtually obstructed so that only a thin catheter can be passed through the stricture, dilatations, with or without an accompanying antireflux procedure, will solve the problem [62]. Antireflux surgery in such situations has markedly decreased over the last number of years, and this may well be due to the newer medications and the more aggressive use of them. The recent successful use of painting the stricture with mitomycin C has also reduced the number of dilatations [42, 67].

In long-term studies of EA and TEF patients, over half had difficulties in swallowing and symptoms of GER, but these symptoms occurred only occasionally and were regarded by most as inconsequential [14]. Pneumonia in these patients is associated with mild long-term lung damage [54].

Tracheomalacia

All babies with EA have some degree (75%) of tracheomalacia (TM), but, like GER, not every TM is symptomatic and needs treatment [39]. Recently, there has been more attention given to the trachea in regard to its relationship to postoperative EA problems. There is now well-documented evidence

(from Sheffield) that in the tracheal area of the TEF there is an area of squamous metaphasia, absence of cilia, and inadequately formed and missing cartilage, which account for the TM and brassy duck-like cough in these infants [84]. This cough is exacerbated by upper respiratory tract infections, which are more numerous because of a local absence of respiratory ciliated columnar epithelium needed to clear the airway of mucus and secretions. The more easily collapsible trachea adds to this problem to a greater or lesser degree. The level of tracheal collapse is usually in the region of the TEF in the distal trachea, at the level of the aortic arch [18, 32, 33, 36, 39, 58, 71]. All of these symptoms (in 10–25 % of postoperative EA and TEF patients) usually occur within the first 2 years of life until the trachea firms up, following which, this is usually no longer a significant problem. If the symptoms are mild to moderate, they do not require surgical treatment, because they tend to improve with time [39].

A small number of these symptomatic 10–25 % of infants some weeks or months after repair have definite sudden respiratory symptoms (or sometimes "dying spells") that are always brought on by feedings and will require repair [18, 32, 33, 36, 39, 58, 71]. The occasional "crib death" has occurred in this group of EA babies with an incidence somewhat greater than chance [60]. During feeds, the distended upper esophageal pouch flattens and obstructs the trachea posteriorly between it and the innominate artery and aortic arch anteriorly (Fig. 35.9a, b). Whether this is actually "reflex apnea" [32] or due to reflux of gastric contents (GER) in small amounts up to the oropharynx and over into the trachea is a good question [60]. The latter theory has also been popular as a cause of the sudden infant death syndrome, and any so-called near miss or dying spell prompts some pediatric surgeons to carry out an antireflux procedure. A full workup, however, should be undertaken to rule out other causes of these spells: neurological and cardiac (vascular ring) as well as airway and esophageal. The telltale x-ray sign of TM is a very narrow upper trachea just below the clavicles seen on a lateral chest x-ray view (Fig. 35.10); however, others argue that this narrowing of the trachea is a common x-ray finding after repair of EA in many infants without any respiratory symptoms.

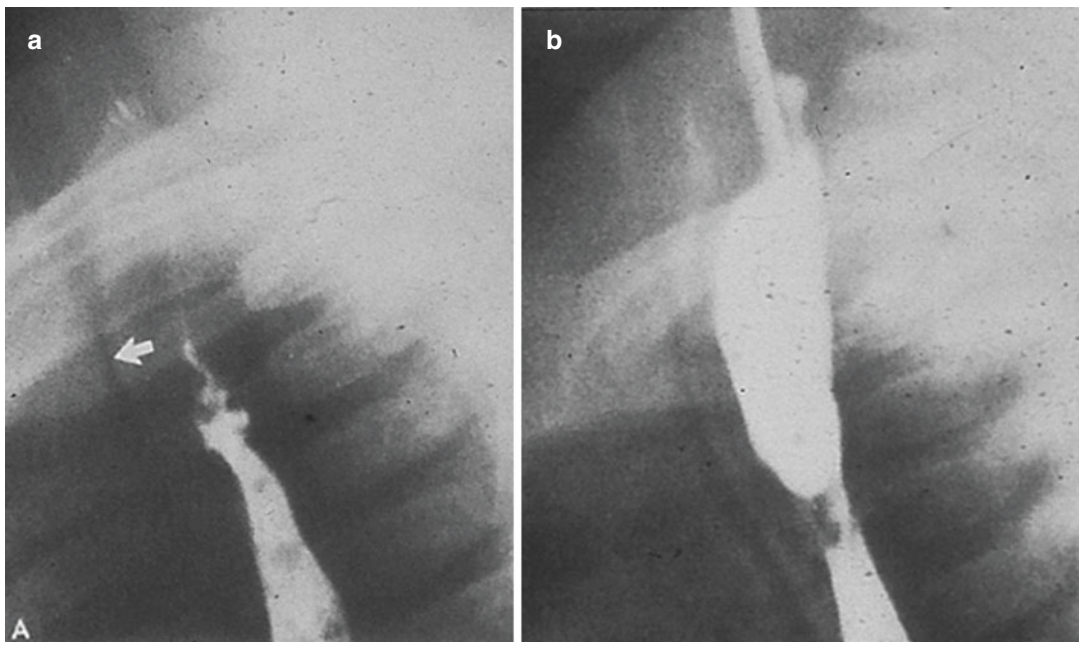

Fig. 35.9 Postoperative EA anastomosis and upper esophagus during contrast esophagram (**a**) which becomes distended during feeds, (**b**) flattening and obstructing the trachea (arrow in figure **a**) between the innominate artery and aortic arch anteriorly and the distended upper esophageal pouch posteriorly

At bronchoscopy the trachea is seen to be narrowed anteroposteriorly to a slit-like aperture, which may be completely obliterated during coughing or straining [18, 32, 33, 36, 39, 58, 71]. The anterior compression is located about 2 cm above the carina and is pulsatile from the aortic arch and innominate artery (Fig. 35.11) [18, 32, 33, 36, 58, 71]. Prior to the 1990s, the treatment for these "dying spells" was to suspend the aortic arch and innominate artery to the back of the sternum (Fig. 35.12a–c), thus pulling the artery forward, and by its posterior attachments to the front of the trachea, the airway was significantly opened up (Fig. 35.12d, e) [18, 32, 33, 36, 58, 71]. The type of operation for a very symptomatic TM that is required in these 5–10 % of EA and TEF repairs is controversial [18, 33, 36, 39, 58, 71] between aortopexy (and innominate artery suspension) from either the right [58] or left [33, 36, 71] chest (transthoracic or extra (retro) pleural), via an upper (limited) sternal split [18] or more recently by endoscopic placement of an intratracheal stent (Fig. 35.13) [33, 34]. Some believe the stent can be used either primarily or if the aortic suspension fails. Since the stents do become somewhat imbedded in the trachea wall and may cause some problems due to granulations, it is still undecided whether they should (or can) be removed at a later (asymptomatic) date in the infant or child's life.

All of this makes one wonder how all these patients with TM were treated over the years prior to the 1980s before the present increase in direct surgical attacks on the trachea and nearby anterior mediastinal arteries. Most of these babies in the past either had long-standing tracheostomies to stent the trachea and/or were fed by either nasogastric tube or gastrostomy (both of which bypass the actual swallowing mechanism said to stimulate the apneic problems), in the hope that in time the tracheal rings would achieve maturity and increase their cartilaginous support [39]. It is interesting that this TM is usually seen in infants and rarely in older children.

There is some evidence that in infants with post-EA major respiratory problems with proven TM and GER, regardless of which is surgically

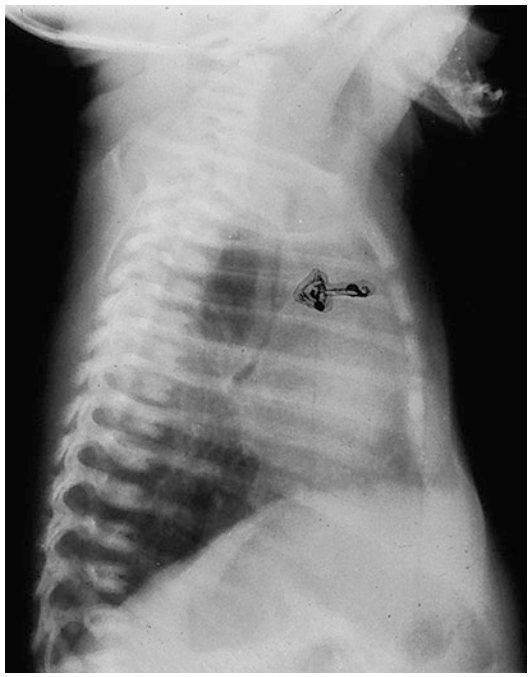

Fig. 35.10 The telltale x-ray sign of TM is a very narrow upper trachea just below the clavicle, seen on a lateral chest x-ray (*arrow*)

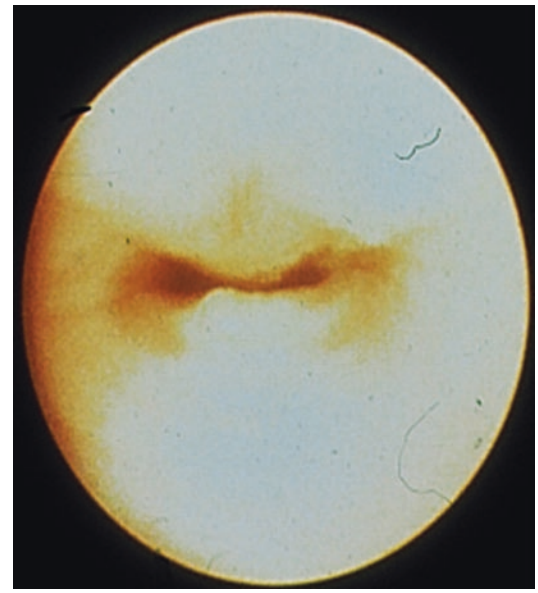

Fig. 35.11 Bronchoscopic view of narrowed trachea anteroposteriorly, which is completely obliterated during cough or straining. The anterior compression is located about 2 cm above the carina and is pulsatile from the innominate artery and aortic arch

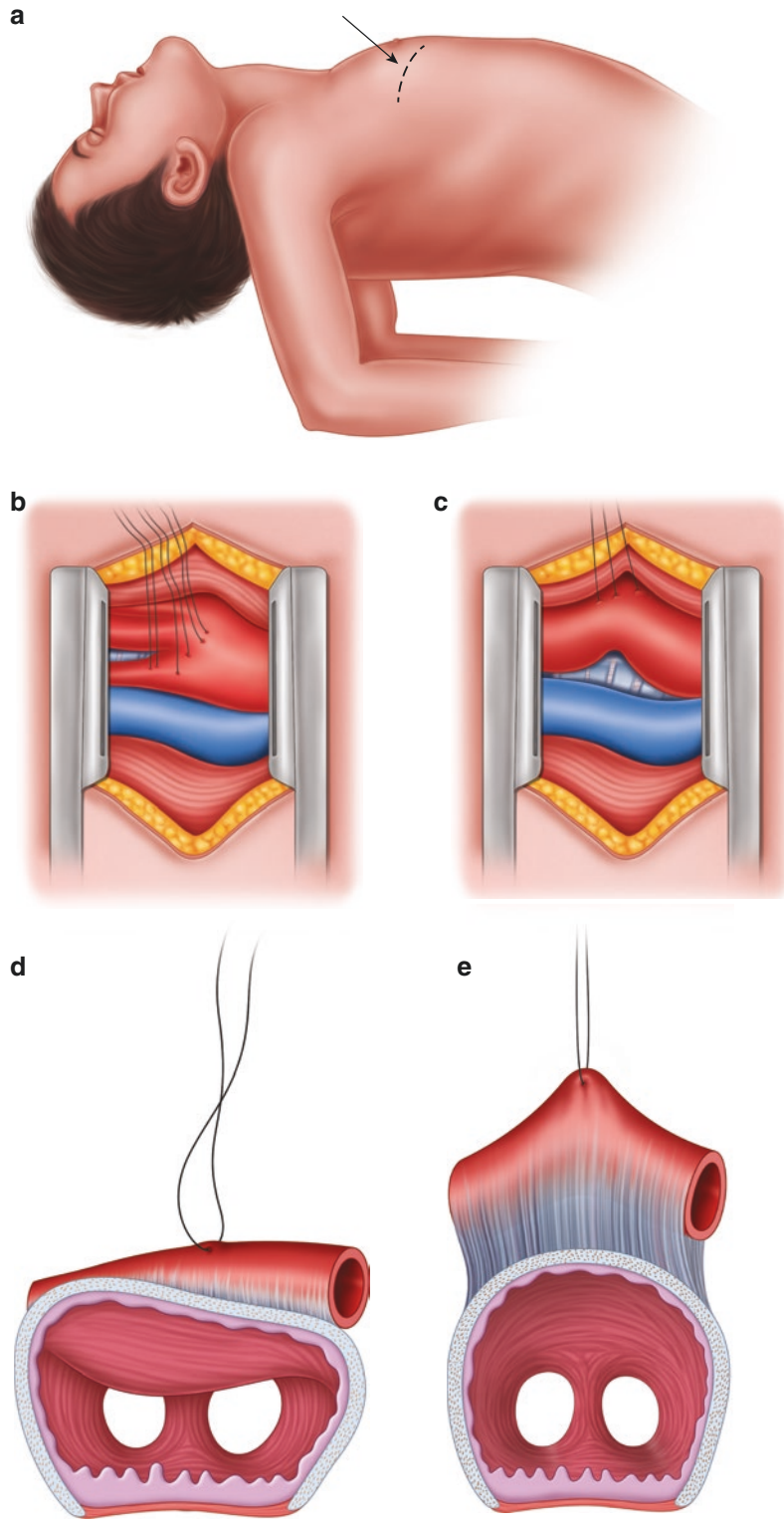

Fig. 35.12 Drawing from Mustard's paper [58] which shows a right extrapleural thoracotomy approach to suspend the innominate artery and aortic arch to the back of the sternum (**a**–**c**) thus pulling these two arteries forward and by their posterior attachment to the front of the trachea, the airway is significantly opened up (**d**, **e**) (With permission from Dr. George Trusler [58])

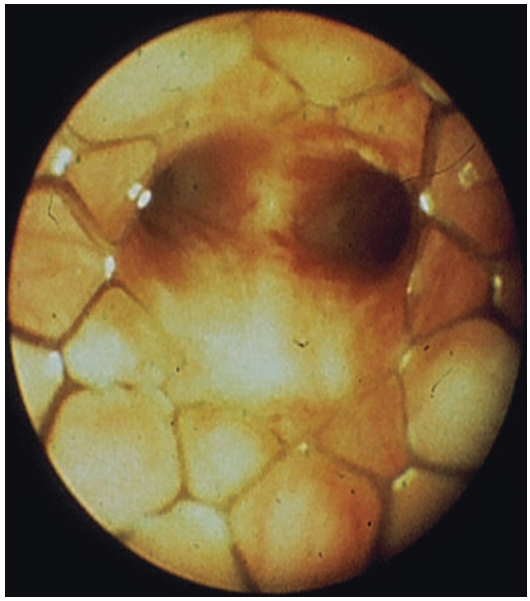

Fig. 35.13 Endotracheal stent can now accomplish the same improved respiratory results. Removal of these stents may be problematic

repaired (according to the preference of the surgeon), one third will have a recurrence of the same severe respiratory symptoms, requiring the other defect also to be surgically repaired. It is presumed that for the infants (mostly) and/or children who were clinically improved with a procedure for correction of TM, the continuing severe GER will be better handled by a noncollapsing trachea. It is similarly presumed that infants who are clinically improved with an antireflux procedure are better able to breathe through their narrow trachea as long as it is kept clear of stomach contents or not compressed by a full esophagus. Therefore, it is difficult to conclude which operation these patients should have first to eliminate their symptoms [60]. In a long-term study of EA and TEF patients, one third had a wheeze and one quarter had at least one episode of bronchitis a year, but these interfered little with their daily activities [14].

Recurrent and/or Missed Tracheoesophageal Fistula

Both of these TEF types present the same way and usually within weeks or months of the original EA repair. They present with coughing, choking, sputtering, and/or turning blue during a feed.

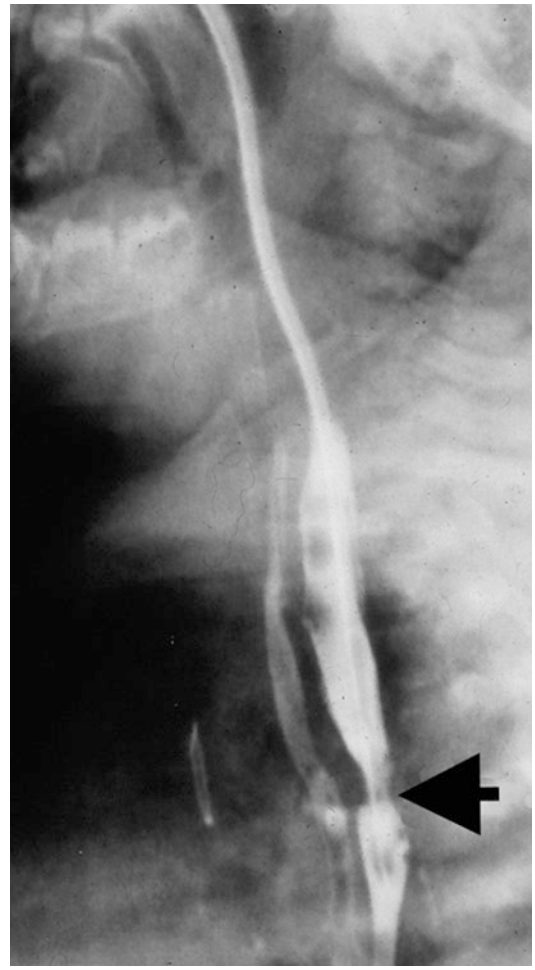

Fig. 35.14 Recurrent TEF (10%) will show up at the anastomotic area (*arrow*). This can be identified by a direct or prone contrast esophagram and/or endoscopy of the trachea

This symptom complex requires immediate attention with a chest x-ray (to rule out pneumonia) and a water-soluble contrast esophagram looking for a TEF, stricture, etc. Although debated by pediatric radiologists, this can be done by a direct esophagram [76] or by a prone esophageal tube pullback esophagram [53] to avoid the mistaken diagnosis, which can occur when contrast enters the trachea from above, rather than through the TEF. Of course, the recurrent TEF will show up at the anastomotic area and occurs in about 10% of repairs (Fig. 35.14) [29]. It can also be diagnosed by tracheal endoscopy. Strangely enough, it seems to occur in the

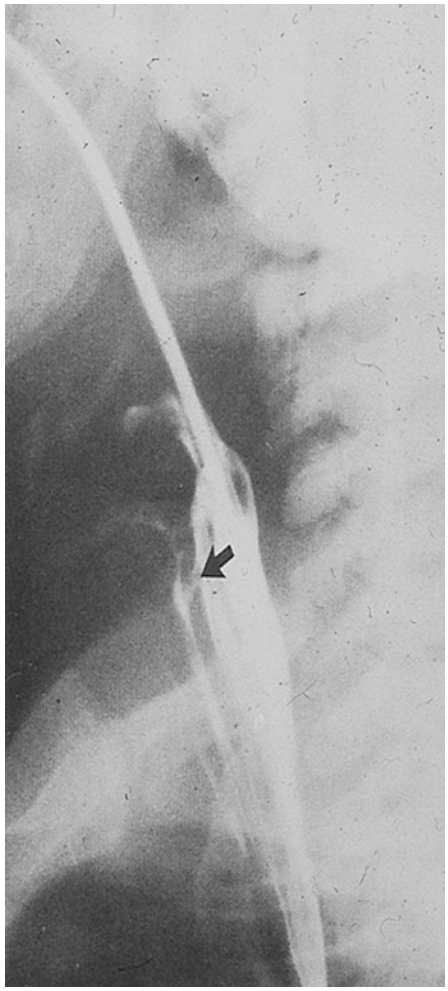

Fig. 35.15 The missed H-TEF (*arrow*) is much higher up at the level of the clavicles. Note that the H-TEF (sometimes referred to as N-TEF) runs upward from the esophagus to the trachea

easy, tension-free anastomosis; the explanation for this is because the anastomosis was not tight, the two suture lines (TEF closure and esophageal anastomosis) are touching, increasing the risk for a stitch abscess or small leak between the two to turn into a recurrent TEF [29].

The missed H-TEF, sometimes referred to as N-TEF (or upper pouch TEF), is much higher up, at the level of the clavicles (Fig. 35.15). It should never be missed if, at the time of the original EA repair, the upper pouch is mobilized up into the neck, staying on the esophagus. If that is done and it is not recognized, the bottom of the H-TEF will inadvertently be cut, making the surgeon incorrectly think that the trachea has been entered; the latter can never happen if one dissects on the esophagus. Be that as it may, these TEFs can be repaired either surgically or glued with or without the help of an ear, nose, and throat (ENT) surgeon and/or IR [11, 13, 83, 86, 87]. The surgical approach to repair the H-TEF is best done through the right neck [11]. Prior to that, some may have an endoscopist pass a soft ureteral catheter through the H-TEF from the tracheal side to more easily identify the fistula (since the fistula runs upward from the esophagus to the trachea; if it ran the opposite way, every time the baby drinks, it would "drown"). After the closure of the two holes (in the trachea and the esophagus), the more mobile esophagus is rotated 90° and stitched in that position so the two suture lines are not "kissing," thus avoiding a recurrent fistula. Occasionally, this high H-TEF is repaired through the right chest, which can be quite technically challenging.

The surgical repair of a recurrent TEF is approached through the original right fourth interspace thoracotomy incision used for the original EA and distal TEF repair, but it is a much more difficult operation than repairing the H-TEF especially since it is the second time around [11, 13, 83, 86, 87]. In both of these types of TEFs, an initial attempt (or 2) at endoscopic closure with glue is well worthwhile.

Of course, the option always exists to endoscope the newborn with an EA prior to the definitive repair to look for another (H-type) TEF [9]; this, however, still does not absolutely guarantee that it will be discovered.

Dysmotility

Early

In the first 3 months or so, there are no problems in swallowing for these neonates because the anastomosis only has to handle fluids. When baby foods are added, some dysphagia may become evident, and this warrants immediate investigation. One should warn parents to slowly increase the quantity and especially the quality of foods given, because, until the anastomosis has matured

and reached its maximal width and until the infant or toddler realizes that he/she will always have to chew their food well, eat slowly, and drink frequently to wash the food down, the parents will have to be the "swallowing conscience" of the child. The parents should be cautioned to call for help whenever the infant coughs, chokes, sputters, or turns blue during or even after feeding.

The early problems that occur from strictures, GER, TM, and recurrent and/or missed TEF have already been discussed, and if all investigations for the above are negative, one must rule out aspiration "over the top" because of muscular incoordination (pharyngoesophageal dyskinesia), which disappears in time, or fatigue aspiration. The term "fatigue aspiration" was coined by the Radiology Department at the Hospital for Sick Children, Toronto, and means aspiration toward the end of a feeding as a result of muscular fatigue. Its treatment is obvious, and it too disappears in time [21].

Late

After the repair has healed, a constant radiological pattern is seen in children who have had the common type of EA with a distal TEF; this was described by Möes (in a paper with Desjardins and Stephens) [23] and expanded upon by Cumming [20]. They noted that when swallowing is initiated, the arrival of the bolus at the lower esophageal sphincter is delayed by a noncontracting segment extending from about 2 cm above to 2 cm below the anastomosis and by a distal (lower) esophageal segment that does not contract until distended. The result is that relaxation of the lower esophageal sphincter, which is supposed to allow the passage of the downward moving food bolus, may have come and gone before the bolus arrives. Relaxation in the absence of a bolus heading down can result in upward reflux of gastric contents, and this may explain why these children often have GER, despite apparently normal lower esophageal sphincter pressures.

This abnormal swallowing pattern must be realized by the parents (and eventually the patient) in simple terms, so that they can deal with the distal dysmotility. Repeatedly warning them to "chew your food well, eat slowly, and drink frequently to wash it down" will stand them in good stead, to both understand and deal with the problem in a reasonable fashion.

Periodically during their teens, for some strange reason, they will have what must be an acute functional obstruction, in which they can swallow only fluids but not solids. Both contrast esophagram and esophagoscopy have shown no foreign body stuck and indeed a wide open anastomosis. These teenagers have come to realize on their own that this is only a temporary functional obstruction at the anastomosis, and after a day or so of fluids, the obstructed feeling will pass, and they will be back to eating normally again. At the best of times, when questioned about it, the older children and teenagers admit they feel the food temporarily hold up at the mid-sternal level (i.e., the anastomosis) in an asymptomatic way, and nothing more than a swallow or two of liquid will wash it down.

Anastomotic Foreign Body Obstruction

Once the anastomosis has reached its acceptable size (by a year or 2), the next problem that commonly occurs is an anastomotic foreign body (FB) obstruction. This happens in 10–15 % of EA repair patients [88]. The infant is now an exploring toddler, often out of the sight of his mother or babysitter, and experimenting with everything, which usually goes into the mouth. The foods that are notorious for causing an acute obstruction (which the parents quickly learn to recognize, because the child suddenly can only tolerate fluids) are lumps of hamburger, hot dog, carrots, potatoes, and bread. The parents must be warned about these notorious foods and told to advance lumpy foods slowly, to see if and when the toddler can tolerate them. If the lumpiness causes dysphagia, they should back off for a few weeks or months, before trying them again. Fortunately, the exploring toddler will quickly learn what he/she can get away with. When there is a history of an acute esophageal obstruction, one must always get a contrast esophagram, first to confirm the suspicion of a FB, and then it can be removed by esophagoscopy under general anesthesia. Fortunately, there are only a handful of "repeat

offenders." It is rare to see this problem occur once the child is in school and even rarer in teenage patients.

Other Complications to Remember

After the repair of the common EA and distal TEF, there is always a small pouch (diverticulum) in the lower part of the trachea usually on the right posterior aspect. This can only cause a problem to the unaware (uninformed) anesthesiologist who is attempting to intubate the infant or child after his/her EA and TEF repair. This pouch, if intubated, will prevent the patient from being ventilated with occasional dire results, if the problem is not recognized. This situation is easily resolved by pulling the endotracheal tube back a few centimeters and then rotating the bevel of the tube to the left so that it can pass into the distal trachea. This pitfall is as potentially disastrous as if the distal TEF is inadvertently intubated prior to repair, which, of course, leads to lack of pulmonary ventilation and instead ventilation and possible perforation of the upper gastrointestinal tract [4]. The solution to the problem aside from its prevention and avoidance is the same as mentioned above.

Postoperative vomiting in the baby or infant who has recently had the repair of EA or EA and TEF is not unusual, and if it occurs, the surgeon often thinks of a cause related to the original surgery. Since pyloric stenosis is more common (1:300) than EA ± TEF (1:5,000), its rare association with the more unusual latter problem is often forgotten [59]. Therefore, once the more common causes for vomiting in the newborn or infant with a recently repaired EA ± TEF (e.g., anastomotic obstruction, GER) are ruled out, pyloric stenosis should not be forgotten.

In a similar situation, the association of EA or EA with TEF and duodenal atresia or duodenal stenosis is well recognized although uncommon; the latter have been reported in 6 % of EA and EA with TEF babies [31]. Quite often, the diagnosis of the congenital duodenal obstruction is not appreciated until esophageal continuity is established and then the vomiting begins. Remembering the possibility is the key to making the diagnosis.

Chest wall deformities develop in one third of babies after a thoracotomy (almost always on the right side) for EA [15]; this is seldom reported. Indeed, it is the thoracotomy rather than the EA repair that is the culprit for the deformity, although an underlying congenital vertebral anomaly increases the risk [15]. The commonest (50 %) deformity is anterior chest wall asymmetry (Fig. 35.16), and it is more common in patients older than 25 years of age. Breast surgery to minimize the inequality may be required in some female patients with extreme asymmetry. The second commonest (10–20 %) is scoliosis, with both asymmetry and scoliosis occurring in about 10–15 % [15]. While scoliosis occurs twice as often in patients with a congenital vertebral anomaly, its incidence in the population is

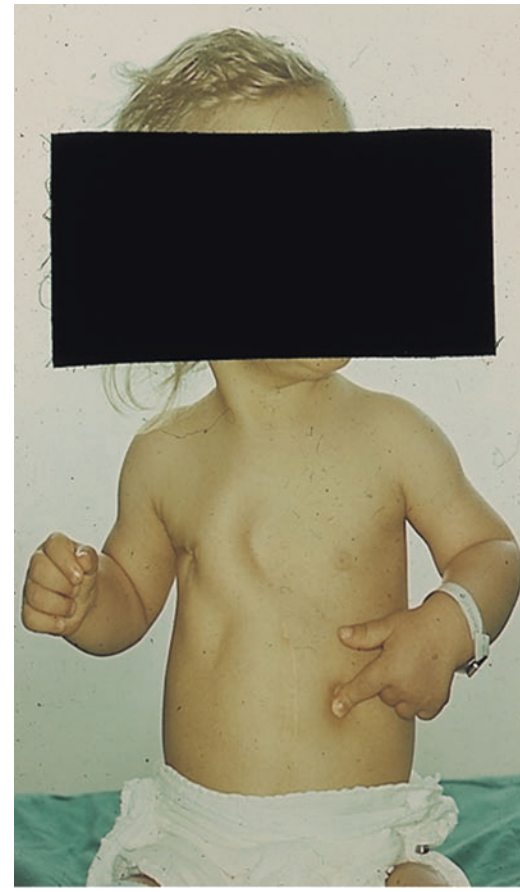

Fig. 35.16 Scoliosis and right chest wall deformity after an EA repair

<2 % [24]. An old classification of thoracoplasty scoliosis (following resection of rib or ribs) or pleural scoliosis (secondary to extensive scarring from chronic infection) confirms the latter to be the cause in the EA situation [24]. The pleural curves have their convexity opposite the right side of involvement. The severe curve only develops in children usually 5 years of more after thoracotomy, with a 10° curve required for the diagnosis of scoliosis [24]. Bracing is suggested for curves that measure more than 20°; if progression occurs in the brace, it should be treated surgically. Its follow-up should be coincident with the long-term EA repair follow-up.

Presently, the thoracoscopic repair of EA and TEF babies can be safely performed by experienced endoscopic surgeons; however, "based on the associated musculo-skeletal problems following thoracotomy, there will likely be long-term benefits for babies with this anomaly undergoing thoracoscopic repair" [43].

Complications Following Esophageal Replacements

Introduction and Philosophy

Although the age-old teaching has always been that the baby's own esophagus is better (repaired) than any other type of swallowing tube that can be made ("The esophagus is certainly better than any substitute for it") [52] and still seems to be "The Golden Rule," one must never lose sight of the fact that the baby with an incompletely formed and/or defective esophagus must never suffer in the long run during our attempt to repair the original esophagus.

Having said that, it is becoming increasingly rare to not be able to save and repair the imperfect esophagus to the end point that it eventually requires replacement. This is mainly due, in part, to many (and continuing) methods (both surgical and nonsurgical) to retain the original esophagus in babies born with the so-called long (wide) gap (usually pure) EA. In addition, an increasing awareness of the damage that results from continuing gastroesophageal reflux (GER) has prevented this problem from irreparably damaging the esophagus, and, as a result, aggressive medical antireflux medications have prevented its permanent damage, and, when they have failed, antireflux surgery has quite nicely reversed the problem successfully [60, 62, 74]. Finally, because of a greater awareness of the preventable causes, which previously contributed to lye and caustic esophageal injuries, these disastrous and long-standing events are now being seen much less frequently [74]. These injuries involving the upper aerodigestive system with scarring of the pharynx, as well as the upper (cervical) esophagus, contribute to the very common postoperative swallowing problems (i.e., aspiration), which are increased when any esophageal replacement is sewn to the pharynx as opposed to the cervical esophagus [26]. Choi et al. [16] stated that "loss of sensation in the hypopharynx and supraglottic larynx plays a major role in the development of aspiration."

In spite of all of the above good news about the successful saving of the pediatric esophagus, there continues to be occasions where the esophagus requires substitution and therein has a major procedure (regardless of the particular substitute) and its inherent complications, which tend to be equally large and at times life threatening. Although most patients have postoperative complications [44], early complications are technical, and most survive [6]. The low mortality (3 %) is notable in relation to the complexity of the cases [44].

Throughout the literature, many words have been used by many authors to describe the same thing; that is another piece of bowel being used in place of the congenitally abnormal (missing) and/or irreversibly damaged pediatric esophagus. Therefore in this chapter, the following terms will be used in an interchangeable fashion to denote the above occurrence: bypass, conduit, graft, interposition, plasty, pull-up, reconstruction, replacement, restoring continuity, substitute, transplant, and transposition.

The new esophageal replacement can be made to replace all of or part of the esophagus, and some can be constructed either in an antiperistaltic or

isoperistaltic fashion. Although some can be placed retrosternally, they have also been positioned in the mediastinum, in either of the pleural cavities and even subcutaneously. If the entire esophagus is not damaged, usually the lower one half needs replacement, and the neoesophagus (constructed through an upper abdominal incision) can be passed through the old esophageal hiatus up into the mediastinum and then anastomosed to the upper one half of the esophagus via a right thoracotomy incision (Ivor Lewis abdominal and right thoracic approach) [12]. These total esophageal replacements can be completed in one stage with an immediate anastomosis between the cervical esophagus and the new esophageal replacement or staged with one or two stomas in the neck. Therefore, depending upon how the new esophagus is made [69] and where it is placed will dictate if, how, when and where the complications present themselves. An example of this is if the replacement is brought up through the left chest, it will have to pass through a small hole in the left hemidiaphragm, which may damage the left phrenic nerve paralyzing the left hemi-diaphragm. If the hole is closed too tightly around the replacement, its blood supply will be compromised. If the hole is left open too widely, then bowel can become incarcerated from the abdomen into the left pleural cavity.

Most of the serious complications occur within 3 years after surgery [55]. Interestingly enough, Raffensperger et al. [65] reported in a large long-term follow-up series that: "The patients with EA with or without an associated TEF consistently have not grown as well as those who required replacement for an acquired condition or injury." However, most of the pediatric patients who receive esophageal replacements tend to fall at or below the 10th percentile for height and weight in long-term follow-up [6].

Generally speaking, the complications of esophageal replacements are related to the actual graft, the most serious of which is that the viability (blood supply) may be compromised to a greater or lesser degree. The next commonest complication is usually found at the esophago-replacement anastomosis (usually in the neck); this is either an anastomotic leak and/or a stricture, often, but not always, related to each other. Strictures are more common in patients who had caustic burns, the latter which often involved the hypopharynx and cervical esophagus above the neck anastomosis [26, 65]. Since these pieces of bowel, wherever they are routed, are aperistaltic (whether anti or isoperistaltic), there are both acute and chronic respiratory problems, as well as the complications that accompany gastro-esophageal reflux (GER). These new esophageal conduits almost always cause feeding problems, in transit of liquids and feeds, which will require tube feeds of some sort for short or long-term lengths of time [6, 27]. Food aversion is also a common postoperative problem [27, 30, 44, 74]. Chronic mucosal inflammation also occurs in the proximal (normal) esophagus, especially where there is GER and/or the stomach is sewn to the proximal (cervical) esophagus. This similar problem also can arise in the distal esophageal remnant (if left in place) following any type of esophageal replacement [72]. GER must be controlled by H_2 blockers and diet to treat a possible end-stage Barrett's syndrome. Barrett's syndrome, usually a later problem (although it has recurred within 7 years of the definitive procedure) is also a possible precursor to later esophageal malignancy, has been sporadically reported in all types of esophageal replacements. Although most series have seen few, if any, cases of Barrett's syndrome [27], some authors have reported significant Barrett's involvement, but there is still indecision in the literature about specific (long-term) follow-up [19, 55, 61].

As with any replacement which occupies the retrosternal space, many surgeons leave in place the original esophagus, especially if damaged by caustic ingestion, with rarely any problems [25–27, 65]. If, however, there are respiratory problems which are hard to explain, one must be aware of the rare occurrence of a piece of retained original esophagus which can act as a blind loop compressing and obstructing the trachea and mediastinal vessels [41]. There is also the rare incidence of carcinoma in the remaining unused esophagus [7].

The one common complication that affects all replacements is the 7 % postoperative adhe-

sive obstruction that occurs after any pediatric laparotomy. Eighty percent of these obstructions happen within the first 2 years after the laparotomy and have the same chance of future recurrences [47, 51].

Each type of esophageal replacement has its own advantages and disadvantages [85]; the fact that there are several types of bowel replacements means that in spite of what is written in the literature in a supportive way for each, there is not really one that is more outstanding than the others. The complications from each type of esophageal replacement will be presented in an order of importance (i.e., quantity and quality). This section focuses on the disadvantages, as they are usually the precursors of the postoperative complications.

Gastric Transposition (Pull-Up)

Gastric transposition (pull-up) has probably replaced the colon as the most commonly used esophageal replacement over the last 20 years [74], but it has the same type and number of complications as all the others. However, it has been reported that these postoperative complications of gastric transposition occur less commonly in children than in adults [57].

The disadvantages of this procedure are directly related to its complications, which are [74]:

1. Stomach in thorax
2. GER
3. Poor gastric emptying
4. Interferes with pulmonary function
5. Delayed growth

As with the other esophageal substitutes, there are certain postoperative complications which are directly related to the route taken for the gastric pull-up, most often in the esophageal bed in the posterior mediastinum. This necessitates removal (either bluntly or by thoracotomy) of the abnormal and/or damaged esophagus [74]. Therefore, the risk of damage to other major organs and/or vessels in that area is significant and not without some risk, especially if blunt dissection is used. Although considered technically easier than a colonic conduit, in gastric pull-ups, postoperative complications are common [44], frequent, and often severe, and many require subsequent surgical procedures. Perioperative (early) complications occur in 52 %; most are respiratory, although significant cardiac arrhythmias requiring medical intervention also develop. Late complications are seen in 64 %, with many of them happening more than 12 months after the patients' definitive repair. These were more commonly gastrointestinal anastomotic stricture (40 %), severe GER requiring an antireflux procedure (15 %), adhesive small bowel obstruction requiring operation (10 %), peritonitis after misplacement of the jejunal feeding tube, anastomotic perforation during removal of impacted food bolus, and traumatic TEF after dilatation of anastomotic stricture [44, 74].

In the immediate postoperative course, because of the retro-tracheal blunt dissection, swelling in that area may cause respiratory compromise, and if not electively done at the end of the operative procedure, tracheal intubation and ventilation may be required for a few days postoperatively. The risk of one or two pneumothoraces is also common.

Esophagogastric anastomotic leaks (12–36 %) as well as strictures (12–49 %) are common in a similar fashion as with other esophageal replacements [74]; however, some authors have reported that gastric transposition patients have significantly less leaks and strictures than gastric tube patients [79]. Nonetheless, their treatment is also similar. Macksood et al. [57] reported that benign stricture, which may occur both early and late, is the commonest problem. Gastric pull-ups (as well as the three other substitutes in this section) have more anastomotic problems with the pediatric patients that had caustic damage to their original esophagus, mainly because the remaining cervical esophagus still has some residual caustic damage, which can start as high as the oropharynx [26, 74].

As with the other esophageal replacements, the gastric transposition patients also experience swallowing problems (30 %) and initially do better with small, frequent feeds [74]. Swallowing improves as the pediatric patient becomes more upright and learns how to feed appropriately with their new swallowing tube. Bilious vomiting, because the

stomach joins the esophagus in the neck and because most of these stomachs have pyloroplasties, is common in the immediate postoperative period, especially if not in an upright position. Because the intrathoracic stomach with its pyloroplasty acts more like a conduit than a gastric reservoir, a dumping syndrome is not unusual (80%), but these symptoms usually resolve within a month or so [74]. These pediatric patients also tend to grow slowly for a few years, but time alone tends to cure this problem; this seems to be one of the hallmarks of all esophageal replacements [74].

Colon

Over the last 20 years, the colon has probably been replaced, as the most popular way of replacing (completely or partly) the inadequately developed and/or damaged pediatric esophagus.

Its disadvantages, which often lead to postoperative complications, are listed as follows [74]:

1. Precarious blood supply
2. Graft necrosis
3. High incidence of leaks and strictures
4. Multiple anastomoses
5. Redundancy over the long term
6. Slow transit
7. Unable to be used if congenital colon problems, which require surgery

Some authors feel colonic conduits overall have a higher complication rate than gastric transposition, but this opinion [44] is not unanimous [78]. Most of the major postoperative complications occur within the first few weeks and are corrected, of necessity, during the first few months after the replacement operation [75].

Generally speaking, there is a higher morbidity rate among patients with the intrathoracic route as opposed to the retrosternal route [75] although some report better functional results with the former [64].

Although there is a small risk of vascular compromise of the colon replacement (especially the right colon), it still remains as the most serious complication of this procedure [56] and more so than in the other type of replacements [2]. If this occurs and there is a neck colonic stoma, it will be obvious; otherwise, it must be suspected if the infant or child is febrile, septic, and/or unwell within the first few days of the operation. Esophagoscopy will confirm graft compromise, and if so, it should be removed and the patient must receive an esophagostomy [56].

The most common complications are anastomotic leakage (6–87%) (especially the neck (esophagocolonic) anastomosis) and stricture formation (0–44%) [74]. The leaks are usually a result of a poor blood supply to the proximal end of the colon, often occur within the first week and resolve within a few weeks; some leaks end up with a stricture, while other strictures occur de novo. These strictures are often cured with multiple dilatations, although some will eventually come to a resection.

As with all esophageal replacements, there is GER, which often causes significant problems of pain, vomiting, ulceration, and stricture. These can be treated medically in the usual fashion, with surgery reserved for the resistant complications. Antireflux procedures will cause an obstruction to an already aperistaltic conduit, so these are seldom done [37, 80]. However, some authors claim their antireflux submucosal cologastric anastomotic gastric tunnel eliminated GER in most of their patients [37]; in spite of this, very few surgeons report success with similar antireflux procedures.

Another common postoperative complication with this type of replacement is redundancy and tortuosity, which increases in time and severity (Fig. 35.17); this not only leads to stasis and delayed emptying but eventually to aspiration, chronic chest problems, and failure to thrive. The position and placement of the colonic replacement are somewhat unrelated to this problem. However, Stone et al. [75] reported that reverse colon segments were more dilated and emptied more slowly, compared to patients with retrosternal colon segments. Nonetheless, if this dilatation and distention problem becomes severe enough, it eventually leads to a localized resection to reduce its length and straighten out the colon tube. Care must be taken in doing this resection as the blood supply is more tenuous than in a gastric tube (GT). If possible, this is

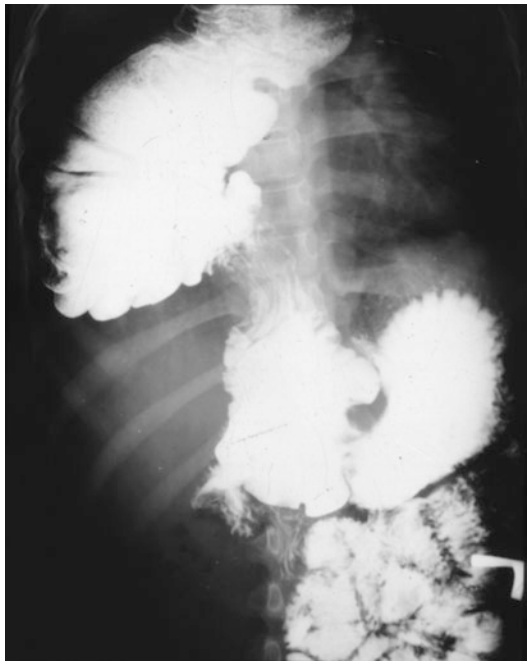

Fig. 35.17 Redundant and tortuous colon replacement; note normal size stomach

most easily done through an upper abdominal incision pulling down and resecting the lower end of the colonic graft and then reanastomosing it to the stomach. This almost always improves the passing of liquids and solids into the stomach. This could possibly be avoided if, at the time of construction of the colon replacement, using a large (? chest) tube as a guide, the antimesenteric half of the graft can be resected so that the piece of colon is narrowed and resembles a GT. Whether this colon will remain as such over the long term is yet to be reported [40]. The chronic lung aspiration (leading to pulmonary restrictive disease in up to 25 %) and nutritional problems due to the colon tube stasis tend to be present during infancy and up to 5–6 years of age, but as these infants and children begin to spend most of their time in an upright position and learn to swallow and eat in accordance with their aperistaltic tube, these problems tend to slowly disappear in most infants and children. Some authors feel that a gastric drainage procedure is an important adjunct in minimizing this long-term morbidity [74].

Although rare, an aortocolonic interposition fistula has been reported (presenting with hematemesis) after 20 years [22].

Gastric Tube

The disadvantages of the gastric tube (GT), which lead to many of the common postoperative complications, are as follows [74]:

1. Very long suture line
2. High incidence of leaks and strictures
3. GER leading to Barrett's syndrome

In spite of the above, some authors believe the GT procedure is easier to perform and has less mortality and fewer complications [27, 30, 35, 70].

Without a doubt, the biggest and most serious complication (albeit rarer than with the other replacements) during or after the construction of a GT is necrosis of part or all of the tube; however, the superior vascularity of the stomach gives rise to less risk than with the colon [35]. The few times that devascularization of the GT has happened were usually intraoperatively, when the gastroepiploic arterial arcade along the greater curvature of the stomach was inadvertently compromised by dividing the omentum too close to the greater curvature of the stomach. The other way that this excellent blood supply for the GT can be compromised is in its compression and/or obstruction in passing the GT up to the neck: either retrosternally (usually) through the mediastinum or through either hemi-diaphragm on its way into the pleural cavity up to or through the supraclavicular space (Sibson's fascia) into the neck. Goon et al. [35] has reported a higher risk of serious chest complications in bringing the GT through the chest with a primary anastomosis in the neck. If there is a primary anastomosis to the proximal esophagus, it will be much harder to recognize a GT which has become partly (usually) at the top (distal end) or completely necrotic. Otherwise, if the GT is staged, then the top will have been brought out as a neck stoma. If the top of an isoperistaltic GT consists of a small portion of distal esophagus (in a wide gap EA), this small piece of distal esophagus, while better to anastomose than a newly formed

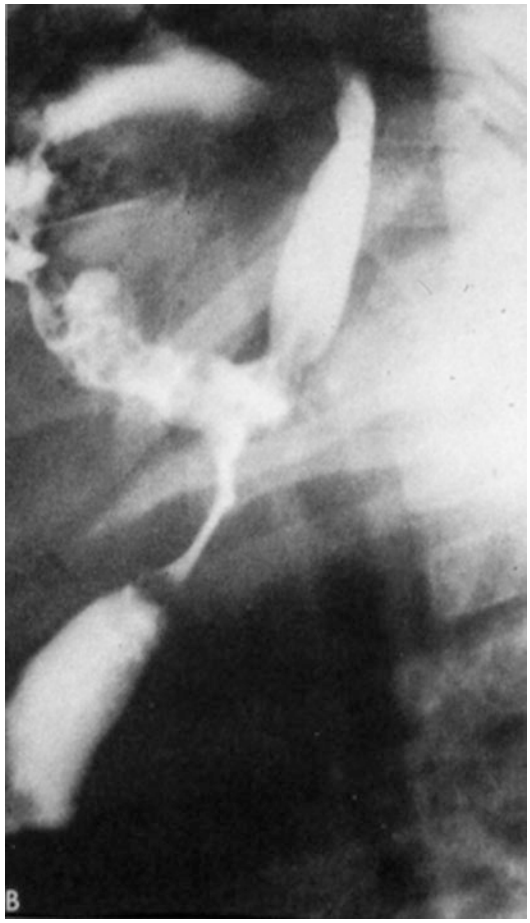

Fig. 35.18 Postoperative leak at esophago-GT neck anastomosis

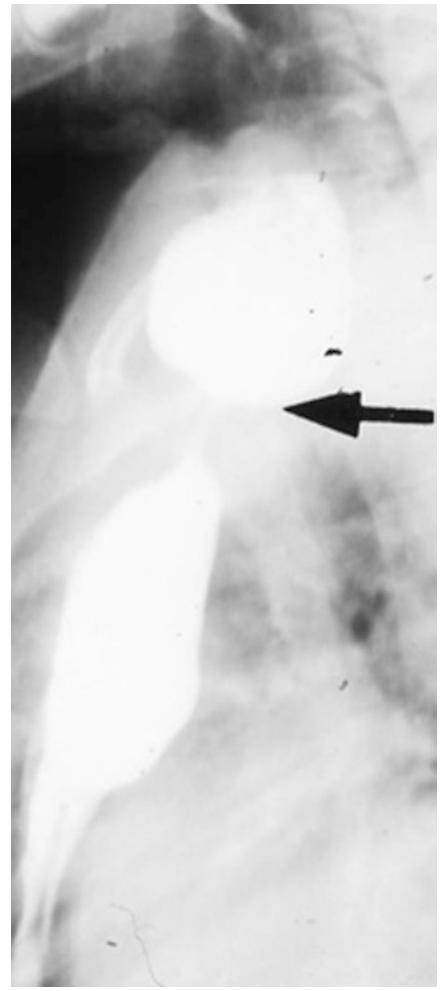

Fig. 35.19 Postoperative stricture at esophago-GT neck anastomosis (*arrow*)

GT, may have a borderline blood supply and as such cause a stricture. If the GT is completed in one stage and part, or all, of it is devascularized, the patient will be febrile and fairly soon septic, prompting one to think about this possible complication.

Generally speaking, the postoperative problems are directly related to the esophago-GT neck anastomosis and its subsequent leak (Fig. 35.18) and/or stricture (Fig. 35.19) [25, 27]. Not all the leaks (33–81 %) result in strictures, and not all the strictures (33–72 %) are preceded by leaks [70, 74]. There does not seem to be a pattern to this problem area at all. It has been reported that a two-layer interrupted anastomosis (along with constant proximal nasopharyngeal sump suction for 1 week) may provide a more problem-free postoperative course [30]. In spite of the above, as well as draining the anastomotic area, it is still impossible to predict an early, late, or no leak, the time of eventual closure of the leak, or the development and severity of any subsequent stricture and the results of its dilatation [27, 30]. If the stricture is so tight that it cannot be dilated at any time and/or it has not been successfully and permanently dilated after 1 year of dilatations, it is time to consider resecting the strictured neck anastomosis [27, 30]. Some resections are now done sooner than later, but the results of this decision remain to be seen. The use

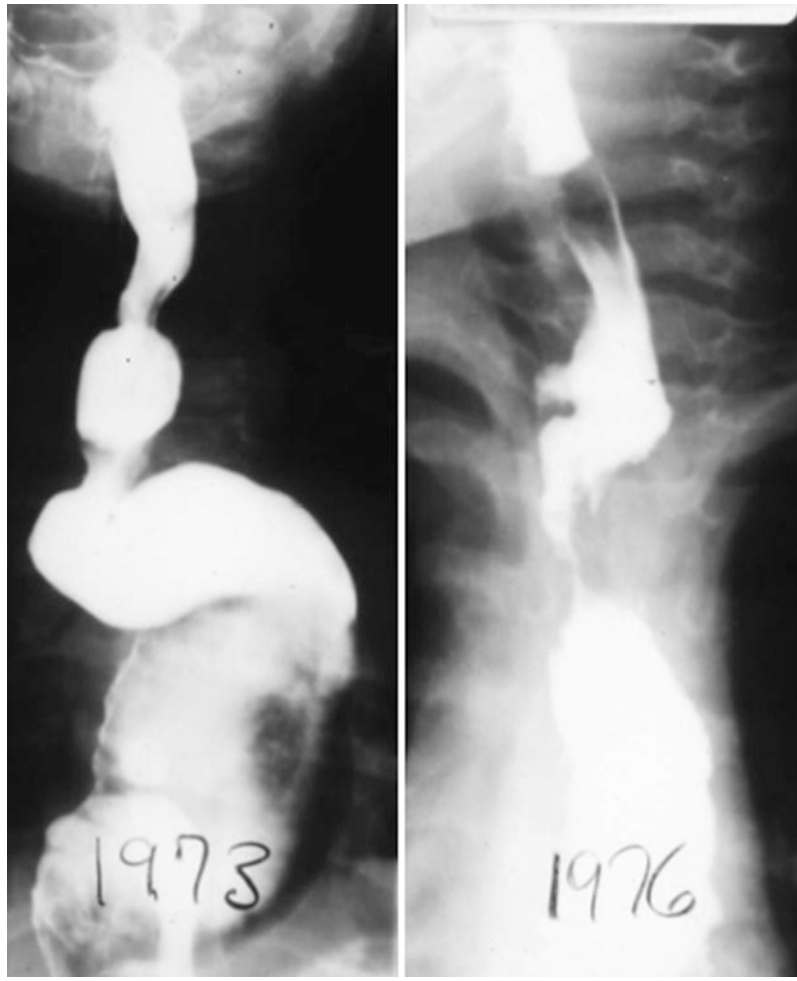

Fig. 35.20 Strictures, dilatation, and tortuosity of lower GT that was cut freehand

of topical mitomycin "C" placed endoscopically may improve the outcome of these strictures [42, 67]. Ten percent of GT neck anastomotic strictures require resection [27, 30].

Strictures of the GT below the neck anastomosis are usually due to the GT being cut or fashioned asymmetrically and probably freehand (Fig. 35.20) [30]. If it causes symptoms and does not respond to dilatations, it will also require a localized resection, but the operative approach will be more difficult.

Redundancy is rarely observed in any GT and is attributed to the thickness of the gastric wall [70]. Another similar complication that can and does rarely arise from a GT cut freehand is a localized dilated area (Fig. 35.20) [30]. This seldom reaches the extent of the dilated, tortuous colon replacement and unless extreme in its tortuosity, rarely, if ever, requires surgical treatment.

A lower stricture may also be due to GER, which can also play havoc with a staged GT construction with its stoma in the neck. In the latter situation, the GER can cause quite severe skin excoriation around the GT neck stoma, which is exacerbated by gastrostomy tube feedings. This annoying problem can be virtually eliminated (or at least minimized) by leaving the gastrostomy to straight drainage and feeding the infant by a gastrojejunostomy or jejunostomy tube [27, 30].

Although all GTs suffer from GER, only a small number have noticeable chronic nighttime coughing and aspiration. This can be, for the

most part, eliminated by keeping the stomach empty for a few hours before bedtime and elevating the head of the bed. Nonetheless, several children do develop chronic respiratory problems and/or failure to thrive (for no apparent clinical reason) until about 5 or 6 years of age, when they suddenly seem to improve [30]. This GER can create a major problem, because the GT, regardless of its construction (ante or isoperistaltic), is really an aperistaltic swallowing tube which empties by gravity; therefore, any type of antireflux procedure would probably obstruct the GT as it enters into the stomach. There have been some reports of prevention of GER without obstruction of the aperistaltic GT by a partial anterior wrap antireflux procedure (Thal, Dor-Nissen) [50, 60] and/or 2–5 cm of intra-abdominal distal GT (due to the increased intra-abdominal pressure) [73]. Aside from the usual medical treatment for GER, if that fails, the best surgical treatment that can decrease the GER is to leave the gastrostomy in place (and frequently open to bedside bag at night), do a pyloroplasty to increase gastric emptying, and/or bypass the stomach for feeding. Fortunately, as the child grows up and spends most of his/her time in an upright position and/or eats more solid food, the GER tends to became much less of a problem [30]. In spite of this, all children with any kind of esophageal reconstructive surgery, especially replacements, must learn to eat slowly, chew their food well, and drink frequently to wash the food down. The incidence of a foreign body (FB) becoming stuck in a GT (or other replacement) is rare and if suspected requires the usual investigation and treatment done for any esophageal FB. The removal from a tortuous GT and/or one in which there is a natural kink or diversion in the cervical region (where the natural posterior esophagus angles anteriorly to join the common retrosternal replacement) may be more difficult.

Chest problems, both acute pneumonia and chronic aspiration from above (more than from below), are not uncommon; especially in the immediate postoperative course [30]. This begins after the esophago-GT neck anastomosis is completed either primarily or secondarily. These infants cannot or will not swallow their saliva immediately after the GT is connected, even when the anastomosis is patent. For this reason, they need constant oral suctioning and/or nasopharyngeal sump suction proximal to the anastomosis for about 1 week [30]. Some infants have chronic swallowing and/or feeding problems, especially if the GT was staged and they did not receive any oral sham feeds; nothing short of time will overcome this type of functional dysphagia. Until such time, gastrostomy or (better) jejunostomy feeds is the only solution [27, 30].

Ulcers (bleeding or perforation) have occasionally been reported both in the GT and the stomach remnant due to stress and/or GER [5]. Occasionally these ulcers do not respond to conservative treatment and require operative repair. While redundancy and partial obstruction with impaired drainage of the GT appear to be etiologic factors, distention of the antral part of the GT may also lead to hyperacidity and play a role in ulcerogenesis [5]. Similarly, a fistula between the GT and the pericardium and/or heart has been rarely reported; it presents with several symptoms and/or signs (chest pain, pericardial tamponade, and upper gastrointestinal bleeding) usually years after the GT was constructed. These complications often present after a significant local infection (empyema, mediastinitis) [27]. If there is a GT fistula with a part of the lung, or the trachea, the presenting symptoms and signs are pulmonary with both air and blood [1, 77, 81].

It is not unusual for the original abnormal esophagus (often from a long stricture due to GER or caustic liquid) to be purposely left behind for technical reasons, with the proximal end closed and the secretions left to drain distally into the gastric remnant. To remove the diseased esophagus can more often than not be very difficult and bloody and remains debatable [6, 27, 30, 65]. The risk of leaving this esophagus in situ in the long term can be the rare closed loop mucocele [41, 49] on either side of a stricture (which requires a segmental resection) and/or the rare esophageal carcinoma in adult life [45].

Although no longer routinely done (for technical reasons), splenectomy is occasionally required, and if so, the patient requires long-term

pneumococcal, *Haemophilus influenzae*, and meningococcal prophylaxis as well as antibiotic coverage to offset the rare but serious post-splenectomy overwhelming sepsis [48].

Jejunum

Jejunum cannot only be used as a true interposition replacing the lower end of the missing and/or damaged esophagus, but it has also been used to replace the entire esophagus. However, it is the most difficult and therefore the least popular procedure done for a missing, malformed, and/or damaged pediatric esophagus [10, 66, 68].

The disadvantages to this use of jejunum (either by pedicle or free graft) are related to its postoperative complications [74]:

1. Precarious blood supply.
2. Microvascular anastomosis (for free graft) and prolonged operating time.
3. High failure rate.
4. Length can be a problem for the complete esophageal replacement.
5. Three anastomoses.

The major complication associated with it, as expected, is its vascular supply and survival of the piece of jejunum. The blood supply, as precarious as it is, either stays intact as a pedicle graft or it is divided as a free graft with an intrathoracic microscopic vascular anastomosis. Either way, "…in children (it) is a demanding operation with considerably early morbidity…" [10].

As with the other three constructed esophageal substitutes, the jejunal one has similar complications to a greater or lesser degree [10, 66, 68]. Once again, depending upon its route of passage, it will also bring into play other specific complications relating to that anatomy (as discussed previously). Leaks (17–25 %) and strictures (6–33 %) also continue to plague this type of replacement and/or interposition [10, 66, 68, 74]. As expected, some strictures, if unremitting to repeated dilatations, will require a localized anastomotic resection [68].

GER also tends to be a problem here with the same type of treatment required; surgical cure is not a guarantee because of the dysfunction of the jejunal graft [68]. However, some authors have reported peristaltic activity with the jejunal graft, which tends to somewhat reduce GER [68]. Chronic respiratory and nutritional problems (all restricting growth) as well as dilatation of the jejunal substitute tend to occur to the same extent as with the colon. Nonetheless, the usual special precautions for drinking and eating must be taught and reinforced to the pediatric recipients of these jejunal grafts.

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The Biology of Stricture Formation After Esophageal Atresia Repair

36

John E. Foker

Introduction

An anastomotic stricture after an apparent satisfactory repair of esophageal atresia (EA) can be a vexing problem for all concerned. Post-repair strictures are common and vary widely in severity; nevertheless, they are important enough that their formation and treatment have been studied by pediatric surgeons and GI specialists. The basic science of wound healing and contraction has also been a fertile research area, very applicable to the clinical situation. Whether from clinical sources or studies of cellular events, the information can provide helpful guidance for the treatment of strictures.

Definition

The definition of a stricture remains imprecise because of the subjectivity of the clinical findings and how they are judged. Even objective signs such as the degree of narrowing on an esophagram have failed to provide agreement on what should be considered a significant stricture. In addition, there is considerable variation in the degree of symptoms that must be present before treatment is recommended as well as what should comprise therapy. Consequently, there is no clear definition of an anastomotic stricture whether described by objective or subjective criteria. Variation in the definitions, the indications for therapy, and even the methods of treatment have not been agreed upon from center to center or even among care providers.

Despite the lack of a uniform definition, it is apparent that stricture formation is a very active biological process triggered by biomechanical factors and the consequences of inflammation on wound healing. Furthermore, there must be essentially equivalent, if opposite, biological changes which occur as the process relents and the stricture fades. Finally, experience also reveals that there is considerable individual variation in the vigor of these reactions. An understanding of the biology underlying the structuring process and its treatment will be helpful to improving therapy.

Treatments

The variations in judging severity carry over into the several aspects of treatment including method, timing, and frequency. At one extreme, some physicians have waited until food sticks before

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doing the next dilation, while our approach, at the other end, has been to dilate earlier and often until evidence for a stricture is eliminated. A good case can be made, we believe, for the apparent absence of symptoms or a stricture or x-ray evaluation as the only satisfactory clinical result. This would begin with the virtual absence of stricture symptoms, although because of the poor function of the lower esophagus in repaired EA and the common presence of a fundoplication in long-gap EA, some degree of dysphagia is often present and complicates the clinical picture [3]. Evaluation will require a normal esophageal contour by contrast study. Consequently, although a stricture is only one component of the dysphagia which is common in adult patients after EA repair, it is one that can be successfully treated.

Strictures are a discrete component of dysphagia; nevertheless, a great deal of variation exists, both in how the strictures are judged and the methods of treatment that are used. Nothing has been settled in the method, technique, frequency, and vigor of dilations, and certainly, issues regarding adding such agents as steroids and mitomycin C or even patching remain open [6]. We believe effective treatment of strictures can usually be achieved.

Stricture formation is a dynamic process, and this chapter will concentrate on the underlying biology to provide information helpful clinically. Treatment is often necessary and we have used a vigorous program of balloon dilations which eventually reach a diameter slightly larger than the esophagus above and below the anastomosis. The over-dilating allows the esophagus to pass solids as normally occurs. This plan of treatment begins with gentle dilations as early as 3 weeks after the anastomosis is created. The dilations are repeated relatively frequently (weekly to biweekly) and with the balloon diameter steadily increased, usually in 2 mm increments to make steady progress. With this approach, the time for restricturing is reduced and, consequently, so is the amount of stricture formed. The trauma of later dilations is also less.

The adjuncts to treatment including steroids and mitomycin C are commonly used, but no agreed upon protocol exists. Nor are improvements reliable achieved. Frequent dilations can now be easily done using an indwelling balloon catheter which can be re-inflated repeatedly. We have also found removable stents placed for 1–2 weeks seem to impede restricturing and encourage it to relent. Although promising, the role of stents and direct injections remain to be determined. This overall regimen has usually been successful; nevertheless, some strictures may remain recalcitrant and resection becomes a better option. The eventual result needs to be a normal esophageal contour by contrast study and the achievement, within a reasonable length of time, the goal of eating normally.

Cellular and Subcellular Factors

With the esophageal ends pulled together, healing by fibroblasts of a roughly circular anastomosis begins and will be followed by some degree of contracture and narrowing. Cellular studies have shown that the anastomotic narrowing results from a series of events beginning with the ingrowth of fibroblasts. Without anastomotic tension, a relatively thin layer of fibroblasts can accomplish the healing. The contraction tendency often normally relents, allowing the anastomotic line to slowly dilate with the drinking of heavy liquids and later with eating solids. In the more routine short-gap EA case, the esophagus may have a normal contour and grow with the child. This is not always the case, however, but the basic and clinical studies on healing have provided useful information on stricturing and what may allow it to relent.

Experimental evidence indicates that the contraction and scar formation which produce the difficult strictures results from activation and further differentiation of the fibroblasts. If the fibroblasts do not further differentiate, stricturing will be much less of a problem and the anastomotic area will remain relatively quiescent. The activation is stimulated by many factors and limiting them should be helpful in lessening this clinical problem.

With increasing tension, more fibroblasts are required, and the factors are set in play which increase the stricturing tendency. Studies have identified some of the triggers for the sequence of

cellular and subcellular events which lead to scar contraction. The sequence begins early in healing with the fibroblasts producing cytoplasmic stress fibers (actins) which turns them into proto-myofibroblasts. With continued stimulation, most importantly from inflammation, the differentiation continues on to the contractile myofibroblasts which also secrete an actively contractile collagen and further increases stricturing. This differentiation sequence results from cytokines commonly released by inflammation, including VEGF and other transforming factors. [1, 2, 9–12, 16, 18, 20–22, 26, 27, 29, 31, 41, 44–46]

This cellular sequence and subcellular events which accompany them are set in motion by biomechanical factors which may be present at the anastomosis site as well as in the repaired esophagus. The first stricture inciting biomechanical factor is anastomotic tension which is well known to surgeons. Although no quantitative studies have been done, it seems likely that there is a correlation between tension and stricturing tendency. Unfortunately, some degree of anastomotic tension is often present in the longer gap repairs. Until there is evidence that an initial period of growth will be sufficiently valuable to incorporate it into the treatment plan for gaps of medium length, tension will continue to be a factor in stricture formation. In order to reduce the differentiation of fibroblasts into myofibroblasts, inflammation and the cytokines it gives off should be minimized. This is most effectively accomplished by establishment of an intact mucosal layer which will minimize inflammation within the esophageal wall caused by tension, pressure necrosis, and reactive sutures. Inflammation and the active stricturing tendency will likely be significant as long as the anastomotic line is not covered by mucosa.

Two common factors after difficult long-gap EA repairs are GER which will increase inflammation at the anastomotic site and stricturing, which when dilated will tend to denude the area and increase local inflammation. Inflammation clearly enhances stricture formation and will be increased by acid reflux up to the anastomotic site. GER is very common after anastomoses under tension and particularly in the long-gap EA group. We have found that the very LG-EA patients for whom a period of growth induction is necessary virtually always have significant GER. Among the several reasons for eliminating GER in the LG-EA group is to reduce stricture formation. The inflammation at the anastomotic site produced by reflux will likely contribute to the stricturing tendency. Without control of the GER, this stimulus to stricturing will continue and even the use of inhibitors of acid production, e.g., proton pump inhibitors, may not effectively control esophageal inflammation. As the DeMeester group has shown, it is bile reflux which is the chief culprit in producing inflammation and both esophagitis and an increased stricturing tendency [4, 7, 13–15, 17–30, 32–40, 42, 43, 47].

The stricturing tendency eventually relents but this process has been less studied, nevertheless, some methods of treating strictures would seem logical as a way to encouraging less stricturing. Our method is to begin early (about 2–3 weeks after the anastomosis), with a gentle balloon dilation to a diameter less than the esophageal lumen. Depending on how much dilation is needed, this is repeated every 1–2 weeks with the balloon increased in diameter by 2 mm each time. Ultimately, we recommend an over-dilation of 2–3 mm to be sure the lumen will easily pass solid foods as the child becomes older.

For the LG-EA group, at least three to four dilations are commonly needed early in the postoperative period and more may be required. To accomplish these dilations, we routinely use balloon dilators under fluoroscopic control. This seems to reduce the trauma of dilation, and, perhaps more importantly, because there is no shearing involved, the mucosa has a better chance to grow over and cover the anastomotic line. With a complete mucosal covering, the inflammation at the healing line of the anastomosis will be significantly reduced.

Clinical Studies of Esophageal Strictures

Clinically, there are both anatomic considerations and surgical principles which have long been known and utilized by pediatric surgeons to limit stricturing [5, 43]. The configuration of the

esophageal anastomosis is usually roughly circular and will heal principally by the action of fibroblasts. Normal healing involves scar formation followed by contraction which for a circular anastomosis means narrowing of the lumen. There are important clinical factors which will increase or decrease this tendency including the size and construction of the anastomosis, the presence or absence of anastomotic tension, and gastroesophageal reflux (GER). These factors have been well described, and the full treatment of EA includes elimination, or at least, minimizing them when significant. The biology of healing, moreover, is quite complex, but this information provides mechanisms behind the promoters of stricturing and in turn guides the reduction of their activity.

When the anastomosis is generous and heals with the aid of fibroblasts that do not become greatly activated, stricturing will be relatively limited. Presumably, this is why for a significant proportion of EA/TEF repairs, in which the two ends are close together pre-repair and GER is limited, stricturing is not vigorous, and, over time, dilation by food and drink will result in an outwardly normal caliber esophagus. These conditions are not always completely met, however, making some degree of stricturing common.

Most of the clinical mechanisms for stricture formation have been well proven or, at least, extensively debated. The more recent work on the cellular mechanisms, however, provided both the basis for stricturing tendency and clues to limit its occurrence.

This very active treatment of strictures seems to have the desired end result. The children in our growth induction treatment of LG-EA did not require dilations beyond the first year or so after the primary repair if the preceding program was followed.

In contrast, we have had a modest experience with patients referred for treatment of a recalcitrant stricture. These patients suggest that the plan of waiting until the patient becomes symptomatic because the stricture is tight, fails because the dilation must be vigorous. This means that, in essence, one is always starting over.

The dilation must be necessarily more dramatic and presumably involves substantial splitting of the esophageal wall in the area of the anastomosis and, presumably, damage to the mucosal covering. As a consequence instead of making progress toward the stricture relenting, it is actively reinvigorated at 2–6 month intervals. By putting together these plans based on the information and clues previously presented, we have developed a plan to actively treat any stricturing tendency and maximize the chance of a very satisfactory and durable outcome.

Our plan, then, follows in this chapter. A typical plan and the various techniques employed include the following:

When the anastomotic size is small, it can result from a narrow esophageal segment, almost always the lower segment, which after anastomosis the tension will be significant and postoperative GER present. Nevertheless, there are details regarding the construction of the anastomosis that will play a role in reducing stricturing. First, if the esophageal ends are small, and typically it is the lower esophagus, and on the back of the upper pouch, the anastomosis will necessarily be narrow. Cutting back (a vertical incision) on the lower esophagus will increase the diameter of the anastomosis and reduce the possibility of a significant stricture even though they will increase the tension.

The lower esophageal segment is also often small in the case of pure EA where there is no lower TEF, and often in these lesions (types A and B), there is usually a long gap between the segments. The long-gap EA (LG-EA) problem can be one of the most difficult repair issues for the pediatric surgeon, and a section of this book presents the issues involved (see Chap. 18). In these cases, the gap poses more of a problem than the potential size of the anastomosis. Narrowing may also be increased by anastomotic tension.

Tension is common in LG-EA repairs. Although tension does cause some narrowing, the advantages of having the esophagus joined outweigh it.

The method of suturing also plays a role. The older technique of two layer repairs not only

was cumbersome but clearly had a higher rate of stricture formation. Currently, anastomoses are almost always done in a single layer fashion; nevertheless, this does not eliminate the occurrence of strictures. The placement of the sutures also will likely have a role. Suturing is a compromise between generous bites of tissue to reduce anastomotic leaks and smaller bites to reduce the amount of tissue caught up in the suturing process which may encroach on the lumen. Large tissue bites, however, will not reliably eliminate leaks and dehiscence and the tying of the sutures becomes the next important factor. If the sutures are tied to just bring the tissues together and not bunch them up, the chance of pressure necrosis resulting in leakage should be reduced, and in turn, the stricturing tendency should be lessened. These techniques are important in performing the anastomosis, but they will not eliminate the possibility of stricturing. Nevertheless, a carefully done anastomosis provides several advantages.

The choice of suture material will also affect the structuring tendency. Reactive sutures, especially silk, are associated with the development of micro abscesses, anastomotic leaks and, therefore, increased stricturing [42]. Absorbable sutures are much better in this regard; however, breakdown by hydrolysis does result in some local reaction. A braided suture, although increasing strength, does promote microabscess formation. Strength does not seem to be an important consideration; the loop of suture will be quite small, and therefore, strong and breakage has not been observed. Our preference has been for fine (5-0 to 7-0) prolene sutures on a small noncutting needle. While prolene is the least reactive of readily available suture material, it does have the drawback of not being absorbed. The sutures themselves will eventually slough into the lumen of the esophagus; however, this may take weeks to months to complete. Because for the LG-EA patients, we do frequent endoscopies to assess the anastomotic site, and also for evidence of GER, many of the prolene sutures are easily removed at that time, for us, the best choice has seemed to be a non-reactive and, therefore, non-absorbable monofilament suture; however, an absorbable monofilament suture may serve equally well.

The stricturing effects of anastomotic tension and the presence of GER make general sense, and now they can be explained in biological terms as to why they increase stricture formation. At the surgical level, however, anastomotic tension frequently provides difficulty in EA repair. It has been a cardinal principle of surgery that an anastomosis should not be done under tension; however, tension is unavoidable in many cases of EA repair. In the earlier days of EA repair, significant tension did produce disastrous results [22]. We learned that a well-constructed anastomosis would withstand substantial tension and it had become increasingly apparent that some degree of tension was often difficult to avoid [8]. Some gaps are just too wide for a primary repair, however, and the ability to reliably induce growth when a long gap exists make a primary repair possible across the EA spectrum. The repair method is quite flexible and using the principle of growth induction will make a primary repair possible. Of interest and value is that growth induction not only lengthens but also greatly widens the small segments. If the tension will be too great for a safe anastomosis, then a week of internal traction of the ends will convert the repair into a more favorable anastomosis. Nevertheless, tension remains a problem in EA repair both for early anastomotic integrity and resulting leaks and later stricture formation [8, 15, 22, 30, 36, 42].

It has also long been known that an anastomotic leak increases the incidence of a significant stricture. Presumably, this results from several factors. A leak implies an area of necrosis and most commonly occurs in an anastomosis under tension. The inflammation produced by these factors will increase the stricturing tendency. A smaller leak will be treated by drainage and will fill in with time, but this process too will narrow the lumen and lead to stricturing. Finally, the presence of a leak restricts dilating and the stricturing tendency will not be countered. Over a few weeks, the stricture may become quite tight.

One of the important factors in healing is the adequacy of the blood supply to the tissues which must heal. A considerable amount has been written about the blood supply of the upper and lower esophageal segments. It is generally agreed that the great majority of the upper pouch blood supply is submucosal and not effected by dissection. Experience has confirmed this and the dissection of many upper pouches has failed to reveal any significant extrinsic blood supply and in no case in our experience was the esophageal tissue compromised. The upper pouches prepared for an anastomosis uniformly look robust and well perfused.

The lower esophageal segment has been the source of considerably more controversy regarding its blood supply. These arterial vessels feed the lower segment in a similar fashion to that provided to the viscera by the abdominal aorta. These vessels are commonly observed during the dissection and recognized as part of the normal blood supply. The question often raised regards the safety of dividing these extrinsic vessels. Often, however, if the lower segment is short, the vessels arise more superiorly and course downward and even with pulling the segments together for the anastomosis; their presence will not hinder the anastomosis. For vessels that limit pulling the segments together, the issue of the necessity of these vessels becomes more important. Both experimental and personal observation, however, has supported the conclusion that the external arteries can be taken if necessary and a submucosal supply will be adequate. Again, no instance in approximately 200 cases was the appearance of the lower segment compromised by dividing extrinsic vessels nor did a resulting necrotic area produce an anastomotic leak. A well-done anastomosis seems to be the best way to accommodate tension and greatly reduce anastomotic leaks; nevertheless, strictures will occur.

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Strictures: Bougienage and Balloon Dilation

37

Khalid M. Khan

Introduction

In adults, esophageal stenosis (narrowing) largely results from malignancy and from strictures due to peptic disease or surgical resection. In children, the main causes of esophageal stenosis are strictures due to ingestion of caustic substances, peptic disease, or after esophageal atresia (EA) repair.

Historically, the earliest treatments included periodic mechanical stretching of the esophagus with bougienage. Dilation is still the most common treatment for patients with esophageal strictures. Stenting can provide luminal structure while the stricture is dilated (discussed elsewhere in the book).

This chapter discusses bougienage and balloon dilation of strictures in children. No specific equipment has been developed for children, and hence, we detail how equipment and techniques can be borrowed from the practice in adults to safely perform dilation and bougienage in small children.

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Etiology

Esophageal strictures are uncommon in children; there are no good data documenting the epidemiology of esophageal strictures in children. Worldwide, the most common cause of esophageal stricturing in children is ingestion of corrosives (typically, of alkali, found in household bleach) [1]. Foreign bodies—particularly certain tablets—can lodge in the esophagus, eventually causing strictures, and are reported in adults or children [2]. Ingested disc batteries typically in infants have been shown to cause major injury, even within a few hours of ingestion. Esophageal stenosis can occur after resection of part of the esophagus; the most common cause is primary repair of esophageal atresia (EA) with or without a tracheoesophageal fistula (TEF) [3]. Peptic esophagitis is a common cause of esophageal stenosis in adults. Both peptic esophagitis and stricture formation are much less common in children. In children, it is most commonly seen in children with neurodevelopmental dysfunction. The prevalence of strictures has markedly decreased as a result of potent acid reduction therapy.

Unlike the adult population where malignancy of the esophagus is increasing, tumors are rarely seen in children and are usually benign [4]. Injury from radiotherapy for esophageal and pharyngeal malignancies is also a cause of proximal esophageal strictures. A review of strictures in adults

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noted that just over half are malignant [5]. Peptic strictures make up two thirds of the benign strictures followed by anastomotic strictures, radiation-induced strictures, and caustic strictures [6–8].

Eosinophilic esophagitis reported elsewhere in this book is increasingly reported in children and adults though exactly how often it causes a true stricture versus dysphagia from an induration and dismotility is not clear. Less common causes of esophageal stenosis in children include congential stenosis (also discussed elsewhere in the book) and rarely systemic sclerosis, epidermolysis bullosa, and, primarily in immunocompromised individuals, infection [9, 10].

Pathophysiology

Esophageal anatomy and function are discussed in detail in other chapters. In brief, it should be noted that the esophagus is a tube consisting of smooth and striated muscle caudally and a mucosal layer; it has no major serosal component. The upper esophageal sphincter (UES) and lower esophageal sphincter (LES) control the movement in and out of the esophagus. The unique function of the esophagus is to propagate food and fluid, through antegrade motility, into the stomach. Esophageal stenosis is therefore of major consequence.

The pathology of stricture formation is understood as a primary response to tissue injury, whether from disease, dissection, or mechanical, chemical, or radiologic insult. In the case of esophageal dissection and reanastomosis, healing is followed by deposition of collagen and consequent fibrosis. Ingestion of disc batteries results in chemical and electrical injury from the change in pH. Congenital stenotic lesions in the esophagus may contain tracheal cartilage [11]. Eosinophilic esophagitis and systemic sclerosis are characterized by marked infiltration, resulting in mural thickening and stiffness. Tumor can infiltrate, fill the lumen with growth, or compress by growth in the esophageal wall or from an external source.

Benign esophageal strictures are often classified as either simple or complex in the adult literature. Simple strictures are characterized by a short, ringlike area, without severe narrowing; the esophagus is fairly normal despite some anastomotic or peptic damage [12]. Complex strictures, in contrast, are refractory to treatment or recur even after being dilated and tend to be longer than 2 cm, angulated, irregular, and severely narrowed, with concentric cicatricial luminal fibrosis but no inflammation, and those close to the UES or LES resulting from radiation therapy [7, 8].

Surgical Anastomosis and Esophageal Atresia Repair

In the alimentary tract, establishing continuity with an end-to-end anastomosis is known to be a potential source of stenosis due to strictures and reduction of lumen size. It is, however, the only option when reestablishing continuity of the esophagus. We have focused on esophageal growth using mechanical traction to for repair of long-gap EA. We have noted, as others have as well, that a long gap that requires tension for primary repair has a greater probability of stricture formation [13, 14]. The tendency to develop strictures has also been associated with an esophageal anastomotic leak or fistula, gastroesophageal reflux, two-layer closure, and certain suture types [13]. The reported incidence varies from 30 % to 50 % in patients with EA; the variation is related to the number of patients with long gaps in any given population [14]. Brown et al. described the relationship between gap length and stricture formation: they found a stricture formation rate of 44 % in a group of infants with long gaps (>3 cm) but only 17 % in the group with short gaps (<1 cm) [15]. Another study determined that anastomotic tension increased the risk of esophageal stenosis by ninefold [13]. The exact pathobiology of stricture formation when tension is applied is not clearly understood. One reasonable possibility is that the blood supply may be compromised when significant tension is placed on the two esophageal ends, resulting in more extensive fibrosis. Of note, in our study of long-gap EA, we showed that esophageal tissue growth is possible when tension on

the esophagus is used to increase the length of the esophagus [14]. Furthermore, we showed that the lengthening of the esophagus does not result in mural fibrosis, but rather a normal mural structure—suggesting that tension may be able to stimulate mural esophageal growth [16].

Evaluation of the Esophagus

In older children and in adults, the typical symptoms of esophageal stenosis include dysphagia, which occurs when 50% of the lumen is narrowed [17]. Other symptoms include food sticking in the chest, chest pain with eating, and either eructation or vomiting of undigested food. In smaller children, reluctance to eat becomes likely; at all ages, weight loss can occur, despite a good appetite or adaptation of diet and eating habits. Respiratory symptoms are also possible, ranging from a cough to pneumonia; an inability to handle secretions implies a severe degree of stenosis.

For patients with symptoms of esophageal stenosis, the most relevant evaluation tool is an upper gastrointestinal contrast exam focusing on the esophageal phase. In patients after EA repair, we have found that instilling contrast directly to fill the esophagus is vital, in order to differentiate true strictures from esophageal dysmotility and to avoid incomplete evaluation from poor filling of the esophagus. The choice of contrast may be determined by the likelihood of other problems, such as the risk of aspiration and the possible presence of fistula in the esophagus.

Cross-sectional imaging with computed tomography (CT) or magnetic resonance imaging (MRI) is useful for evaluation of esophageal masses. Endoscopy is essential in evaluating the possibility of reflux-related esophagitis, along with a contrast exam, pH determination, and an impedance study for evaluation of gastroesophageal reflux. We have also used endoscopy for sizing the strictured area and assessing esophageal length; the presence of a hiatal hernia and the esophageal histology results will help diagnose eosinophilia. High-resolution endoscopic ultrasonography (EUS) can help define the length of the fibrous scar and the extent of eosinophilic thickening of the esophagus [18].

As a component of the differential diagnosis of patients with esophageal symptoms, an assessment of esophageal motility may be prudent, especially if the diagnosis is unclear. Such an assessment is the standard method of diagnosing achalasia of the lower esophagus. In a study of symptomatic patients with eosinophilic esophagitis, the investigators used a pull-through balloon technique to identify the area needing dilation [19]. If the etiologic diagnosis of congenital esophageal stenosis is unclear, EUS is useful in differentiating tracheobronchial remnants from fibromuscular stenosis [18, 20].

Management of Esophageal Strictures

The principle of nonsurgical treatment of enteric strictures has been based on application of luminal circumferential force, to disrupt fibrous tissue that constitutes the stricturing process [7, 21]. The configuration of the force can be tangential, shearing, or direct—depending on the instrument used [21]. Electrocautery can be used to ablate tissue or to excise fibrous tissue, with injection of steroids and application of mitomycin C used as adjuncts to reduce the possibility of stricture recurrence [22]. High-dose systemic steroids have been shown to be useful for preventing stricture formation after extensive mucosal resection of Barrett's lesions [23].

To treat patients with stenotic esophageal lesions, the usual timing of intervention is determined by the development of symptoms. However, the need for intervention can be anticipated in some circumstances, such as after an anastomosis has been created or after ingestion of a corrosive substance. In our patients with long-gap EA, we have hypothesized that the risk of stricture formation is high and that the timing of esophageal dilation should preempt severe stricture formation [24]. Conversely, other investigators managing EA have found it better to wait and see if symptoms develop; their practice is clearly still the standard when managing

the typical anastomosis, both in children and adults [1]. Similarly in treating adults with benign lesions, opinions also differ: some prefer intervening early, but others favor allowing a scar to be established before disrupting it [24]. In a study of balloon dilation of post-anastomotic strictures, early dilation was associated with less subsequent dilation [25].

Bougies and Balloons

The concept of bougienage dates back to the Middle Ages when candle wax, bone, silk, and cork were used to deal with food impaction.

The last 50 years have seen a number of developments in the clinicians' ability to dilate. Mercury-filled dilators, most notably the Maloney dilator, have been shown to be highly effective; they can be used blindly and even for self-bougienage [21]. Currently, the most common method used in the United States is a system of long, tapered radiopaque, polyvinyl hollow tubes such as the Savary-Gilliard system (Cook Endoscopy, Winston-Salem, NC) [12]. Regardless of the make, bougies come in a range of diameters up to around 20 mm; the extent of dilation is aimed at restoring the normal diameter of the esophagus.

Balloons constructed from polyethylene or related materials that can fit through endoscopic channels or over a guidewire are an alternative to bougienage. They come in a range of lengths and diameters. The balloons can be employed endoscopically or radiologically and expanded using contrast to ensure accurate positioning. In contrast to bougies which produce a shearing force, balloon dilators deliver a radial force, resulting in a simultaneously applied dilating force across the entire length of the balloon and thus the stricture [6, 8].

Technical Considerations

In adults, dilation with a bougie device can be performed blindly. But the typical dilation is more safely managed using radiography or endoscopy, with or without placement of a guidewire, with the patient under sedation. The size of the lumen that is aimed for varies, but 15–20 mm is necessary for symptomatic relief in adults.

To minimize the risk of perforation, 3 mm of dilation in a single session, with a limit to a diameter of 15 mm, has been advocated in adults, and multiple sessions may be necessary for symptomatic relief [12, 26]. A stricture can be considered refractory to dilation if a diameter of 14 mm cannot be reached during five sessions at 2-week intervals and recurrent if a satisfactory luminal diameter (14 mm) cannot be maintained for 4 weeks [12, 26]. Tight strictures may require redilation at frequent intervals, while rings and webs can be disrupted relatively easily with a larger diameter balloon [12, 27]. In patients with achalasia of the distal esophagus, the principle is to use a large balloon to split the muscular layers. The length of time that a balloon should be inflated is not agreed upon. It ranges from short bursts of 20–30 s to maintaining inflation for several minutes.

As advocated for complex benign strictures in adults, we recommend fluoroscopy and endoscopy in pediatric patients with benign strictures [1]. In infants, bougienage is often performed blindly after EA repair or during procedures involving long strictures from caustic ingestion. In certain patients recovering from caustic ingestion, long-term care has involved antegrade and retrograde dilation, often self-performed [28, 29]. We would add a note of caution when using tapered bougies in small children with a Nissen fundoplication: the bougie often needs to be driven down into the stomach, so the fundoplication may be inadvertently dilated, especially if the stricture is close to LES.

No balloons have specifically been created for pediatric patients; however, esophageal balloons can be used in older children without difficulty. In infants, the standard endoscope diameter may be too large for the esophagus, so we use a smaller-caliber endoscope typically 5–6 mm diameter. These scopes have a channel of only 2 mm which is too small to pass endoscopic balloons. We therefore pass the dilator alongside the endoscope and position it under direct vision.

In small children, esophageal balloons should be used with caution: the infant esophagus is roughly the same as the length of standard esophageal balloon and the balloon may inadvertently disrupt the UES or LES or fundoplication similar to the use of tapered bougies. Measurement techniques can be used to estimate the length of the esophagus before dilation. We have adapted to using shorter balloons designed for the pylorus and the colon that are about 5 cm in length (Fig. 37.1). The smaller length, however, poses the risk that the balloon will slip and hence lose position. The length of the balloon is also important when it comes to dilating a particularly angulated area: balloons are designed to expand in a linear fashion and may disrupt the adjacent mural structure, and polyvinyl tapered dilators may be the safest option.

In the most severe strictures and those affecting the cervical esophagus, a combination of antegrade and retrograde endoscopy has been described in adults with very tight strictures [30, 31]. We have used dual endoscopic access to the proximal and distal end of the stricture, by accessing a gastrostomy with a small scope (Fig. 37.2). A guidewire can be passed using fluoroscopic guidance; even a precut knife can be used to provide a small access hole in the stricture [32].

Outcomes

Objective outcome measures of dilation include improvement of symptoms, the need for redilation, and, in patients with benign strictures, the number of dilations necessary. In adult patients with peptic strictures, symptomatic response rate is 100 %, even though up to 80 % of them may need redilation in the subsequent year; moreover, the need for a second dilation is predictive of the need for further dilations; this is similar to postanastomotic strictures [25]. The use of acid blockers and especially proton pump inhibitors has reduced the restricture rate.

In a randomized prospective study of patients with peptic esophageal strictures, both polyvinyl bougies (Savary-Gilliard) passed over a guidewire and through-the-scope balloons were effective in relieving dysphagia, but the balloons may have had a long-term advantage [33]. In a long-term study of bougie versus balloon dilation, the investigators initially found an increased duration of symptom relief at 5 months with bougies, but

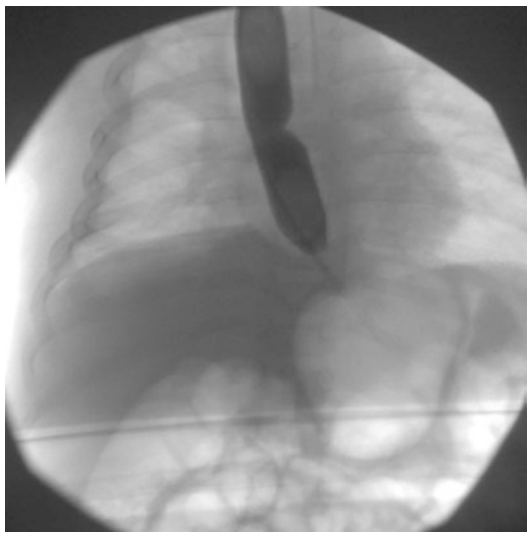

Fig. 37.1 Balloon dilator used in an infant. Note the proportionally larger diameter of the balloon to the thorax. The lower end is sitting above the esophagogastric junction. The patient is monitored for airway compression throughout the procedure

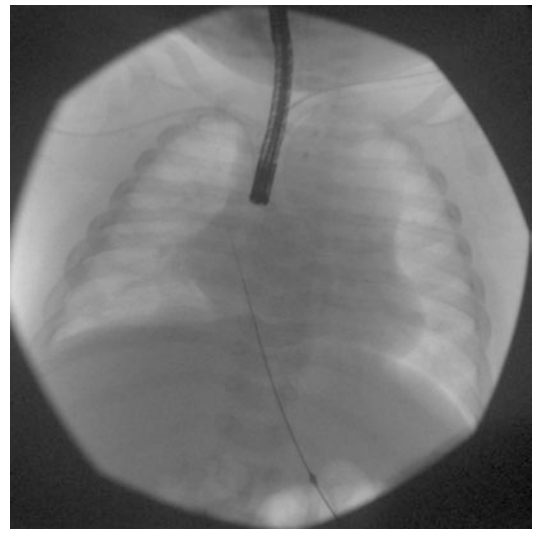

Fig. 37.2 Shows the relationship between the endoscope and a balloon dilator advanced through the gastrostomy site during retrograde balloon placement

at 1 year, there was no difference [34]. In a study of patients with peptic strictures and Schatzki rings, Scolapio et al. observed no differences between Savary-Gilliard versus balloon dilation in the relief of dysphagia or in the need for repeat dilation [26]. An advantage of Savary-Gilliard dilators is that they are reusable [4].

In children, there has been extensive use of bougienage for corrosive injury. Particularly long segments should be dilated with bougienage, and retrograde dilation and self-dilation with bougies is well described [35]. In one series, early dilation was associated with fewer complications than delayed dilation [36]. Similarly Contini et al. [37] found that those referred late had more complications and required more dilations. A study of balloon dilation for corrosive injury in children showed adequate palliation but no avoidance of surgery [38]. A study of long-term outcome of peptic strictures found that recurrent dilation was a predictor for the need for surgery [39]. Ultimately, these data indicate that the degree of fibrosis as the major determinant for the need for repeat dilations.

Bougienage has been shown to be effective in strictures that develop after EA repair, with an 87 % success rate reported in one series [13]. A single balloon dilation has been shown to be successful in one third to 100 % of patients [3, 40–42]. Koivusalo et al. found that a wait-and-see policy based on clinical indications was superior to routine dilations; over 50 % of their patients did not require dilations at all [43]. Most of the above studies did not include a large number of long-gap EA patients that have the greatest chance of recalcitrant strictures. In a retrospective pediatric study, balloons were more effective than bougienage and required fewer dilations [3].

The efficacy of dilation seems to be limited, and with a significant chance of esophageal rupture in congenital strictures that include cartilage, surgical resection may need be considered in such patients [44].

Adjuvant Therapy

Steroid injection into a fibrotic stricture has been shown to reduce stricture recurrence; 4-quadrant injection of diluted triamcinolone acetonide with a sclerotherapy needle was effective in 71 patients with various types of benign esophageal strictures [45]. In a randomized study of triamcinolone with dilation versus dilation alone, the interval between balloon dilations was increased with steroid injection [46]. A similar protocol that added antacid therapy with steroids further reduced the redilation rate and without perforation [47]. High-dose dexamethasone has proven to reduce the number of dilations required [48]. Ultimately, the effectiveness of steroids is likely to be related to the degree of inflammation [12]. In contrast, mitomycin C reduces the risk of stricture formation by reducing fibrotic tendency [22].

Complications

The risks and benefits of dilation—including those related to endoscopy, radiation, anesthesia, and existing comorbidities—must be explained to the patient and/or parent in order to obtain informed consent. The contraindications are relative and include a compromised airway, bleeding potential, and the general condition of the patient to undergo procedures and to blind bougienage include mucosal bridging, pseudodiverticuli, fibrotic shelves, as well as those described as complex benign strictures.

Esophageal dilation should be discussed with the patient and/or parent prior to the procedure using the best available data to estimate risk and benefit. Antibiotic prophylaxis is recommended in high-risk patients undergoing stricture dilation as there is an increased likelihood of bacteremia with dilation of tight strictures [49].

In adults, the most frequently reported complications of stricture dilation include perforation, hemorrhage, and bacteremia [50, 51]. The risk of perforation increases with larger, more sclerotic, or angulated strictures; with more aggressive dilation; after radiotherapy and with the preexistence of large hiatal hernias. Aggressive dilation of eosinophilic esophagitis lesions also risks the possibility of perforation. In a retrospective analysis of mercury-filled bougies, wire-guided polyvinyl bougies, and through-the-scope balloon dilators in adult patients, 4 perforations were noted in 348 procedures, and all of these were from blind dilation

of complex strictures with a mercury device [51]. A review of 251 procedures comparing the Savary-Gilliard system versus balloons also found no difference in complication rates [26]. Similarly an early prospective study of bougies versus balloons in adults found no difference between the two methods [52]. The investigators estimated a serious complication (perforation) rate of 0.4 % and minor complication rate of 4 %, the majority of the latter with repeated bougienage. Overall there is no significant difference between the two methods [5, 34]. A study of the degree of mural disruption with balloon dilation found that 21 % of patients experienced esophageal ruptures, mostly intramural tears; most of the injuries to the esophagus were not clinically relevant [53]. The cervical esophagus and the area immediately above the stricture are usually the sites of perforation.

Repeated dilation of corrosive ingestion was associated with a perforation rate of 17.4 % in one series from Turkey [54]. Other series describing dilation of strictures in children have noted perforation rates less than 3 % after balloon dilation and under 10 % for bougienage [3, 55–57]. Thus, balloon dilation may be preferable in children with simple strictures. In small children, the procedure is invariably performed under general anesthesia, so potential complications of anesthesia have to be anticipated. Anesthesiologists should keep in mind the possibility of hemodynamic instability and of endotracheal tube tip obstruction by the inflated balloon and anesthesiologists should safeguard the airway against blood, secretions, and radiopaque fluid during esophageal balloon dilation [58]. Mediastinal compression during the procedure should be identifiable and corrective action taken [3].

Summary

Esophageal strictures are uncommon in children. Noninvasive management of esophageal strictures is based on the same principles in adults and children though there is much less published literature in pediatric practice. Nevertheless, bougies and balloons can be effectively used to manage benign esophageal strictures in children.

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The Dynamic Stent in the Treatment of Oesophageal Strictures

38

Luigi Dall'Oglio

Introduction

Conservative management of cicatricial oesophageal strictures (OS) includes oesophageal dilations and pharmacological therapy. Balloon dilation or endoscopic bougienage is the traditional treatment for OS. Safety and success rate, the optimal duration and the type of dilation remain controversial with a well-known risk of stricture relapse [1, 2]. Oesophageal perforations during endoscopic dilations of caustic stenosis are reported in as much as 15–20 % of patients in large series [3].

Oesophageal stents became popular in the last decade for the treatment of benign OS. Stenting represents a new strategy in order to avoid multiple dilations due to stenosis relapse; it is less invasive than surgical replacement procedures and recurrent endoscopic dilations. Several authors described their experience with different types of stents: silicon stent [4], self-expanding covered stent-Polyflex-Rush [5, 6], retrievable covered self-expanding metal stents designed for tracheo-bronchial use [7], polytetrafluorethylene stent [8], silicon stent [9, 10] and self-expandable biodegradable stent [11].

One advantage of stents is the potential for oesophageal function to be maintained. Stents may have two different mechanisms of action to achieve this; one type of stent, such as Polyflex or self-expanding metal stents, allows the passage of food inside the stent [5–7], while in the second type, i.e. the dynamic stent discussed here, food passes between the stent and the oesophageal wall [1, 8–10]. We have previously demonstrated effectiveness and safety of our custom silicone stent either for the number of dilations or for the duration of the treatment, in comparison with the traditional strategy of repeated oesophageal dilations [1, 9]. More recently, we have demonstrated success of the dynamic effect of our stent in caustic and post-oesophageal atresia strictures [10].

Stent Use in Children

Broto et al. [6] published a series of ten patients with recalcitrant strictures who were managed by a self-expanding silicone/polypropylene oesophageal stent (Polyflex). The stent was kept in place for 20–133 days and allowed normal feeding, and its tolerance was excellent. In this study, five patients were completely cured with a follow-up from 4 to 19 months. Stenting treatment reduced the treatment time and avoided the repeated anaesthesia sessions necessary for dilations. This stent represented an improvement in the treatment of children with benign OS because of its tolerance by patients and their families. The

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absence of the NGT seemed to be very important; however, the risk of stent migration and adhesion was significant [12]. In his review, Kramer compared published series that included paediatric patients that had undergone stent treatment [12]. The migration rate was reportedly 10–29 % for the expandable stents and 0–5 % for other intraluminal stents, like the dynamic stent. Effectiveness of the expandable stents was reported in 50 % and 85 % of the patients, respectively. In series describing the use of expandable stents, De Peppo, Atabek and Mutaf [8, 9, 13] reported healing of the strictures with intraluminal stents in 96 %, 72 % and 69 % of patients. We interpret these reports as suggesting that the dynamic effect of food passage between the stent and the oesophageal wall allows for the improvement of oesophageal motility in addition to preventing stricture recurrence. In our last publication about dynamic stents [10], we reported good results in 88.6 % of the patients. The reduction of the stricture healing rate, in comparison to our previous paper [9], is due to the enrolment, from other referral centres, of very severe OS cases in which the stent had been used as rescue therapy before surgery.

The Dynamic Stent

The custom stent is built coaxially over a 12–14-Fr nasogastric tube (NGT) that helps to maintain the correct position. We use slices of silicone tubes (Penrose Drainage Redax S.r.L. Mirandola, Mo, Italy) that overlap each other to reach the desired diameter and length (Fig. 38.1). The custom silicon stent, which has a 6.5, 8.5, 10.5 or 12.5 mm external diameter according to the patient age and stricture length, is tailored to exceed the length of the stricture by at least 2 cm to avoid displacement of the stent above or below the area of interest [10]. The two stent ends are tapered for its easy introduction and to allow the food passage between the stent and the oesophageal wall. Instead of the silicone slices, a radio-opaque band is used to improve the radiological image during the insertion procedure and to evaluate the stent position; two metallic clips are affixed at the extremities. The patented commercial version of the dynamic stent will have the opportunity to vary the rigidity of the stent itself.

How the Dynamic Stent Is Used

The dynamic stent placement requires an experienced endoscopic team and a meticulous attention to all phases of our protocol. Endoscopic procedure is performed under general anaesthesia with tracheal intubation. We use standard videoendoscopes (GIF-XP160, GIF N180 and GIF-Q165; Olympus Europe). A straight-tip stiff guide wire (Amplatz Super Stiff, 0,035 in, Boston Scientific, MA, USA) with a semi-rigid tip is inserted through the stricture in to the stomach under spot fluoroscopy. Subsequently, oesophageal dilations are performed with an endoscope balloon dilator (TTS Microvasive, Boston Scientific from 10 to 12 mm in diameter) or Savary-Gilliard dilators (5, 7, 9, 11 and 12.8) (Cook Medical, Bloomington,

Fig. 38.1 The dynamic stent in the custom version. The two extremities are tapered for easy insertion and food passage around the stent

IN, USA) to obtain an adequate oesophageal calibre that would allow stent placement, of the desired size. Either the proximal or distal ends of the stricture are marked with a cutaneous marker (Fig. 38.2). After the dilation, accurate endoscopic evaluation of the oesophageal wall is performed with water injection and the aspiration of blood and mucus. We rule out oesophageal perforation with water-soluble contrast medium injected through the endoscopic channel with air under pressure (Fig. 38.3). A minimal perforation does not represent a contraindication to stent placement. The stent is then inserted through the mouth, over the guide wire, and its correct position is radiologically confirmed. The nasogastric tube of the stent is then passed backward through the nasopharynx and out of the nose, to which it is fastened. To avoid the distal displacement of the stent, a transverse silicone bar is affixed to the nasogastric tube outside the nose (Fig. 38.4). The patient receives a standard antibiotic prophylaxis, post-operative sedation and i.v. omeprazol treatment (1 mg/kg/day).

On the first post-operative day, an oesophagram (Fig. 38.5) with water-soluble contrast medium is performed, and, in the absence of leakage, oral, cold soft feed is started. In the absence of a perforation, the patient receives dexamethasone (2 mg/kg/day) for 3 days, progressively reduced and stopped in 6 days. Drooling and retching are always present on the first day after stent placement but resolve spontaneously, and all patients are generally able to resume a normal diet. In a few days, patients are gradually encouraged to eat normal food. We suggest solid food if the child is able to handle it. Patients are allowed to graduate from semi-liquid to soft or normal food (such as meat, pasta and pizza) according to their age, psychological condition and the characteristics of the stricture. The ability to eat normal food represents a very important and positive prognostic factor. Early resumption of oral feeding may be effective in

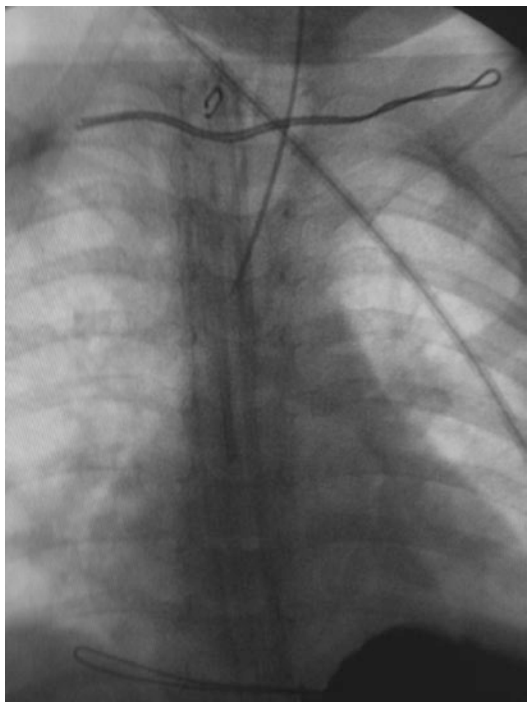

Fig. 38.2 Cutaneous marks at the stricture extremity, endoscopically and radiologically evidenced

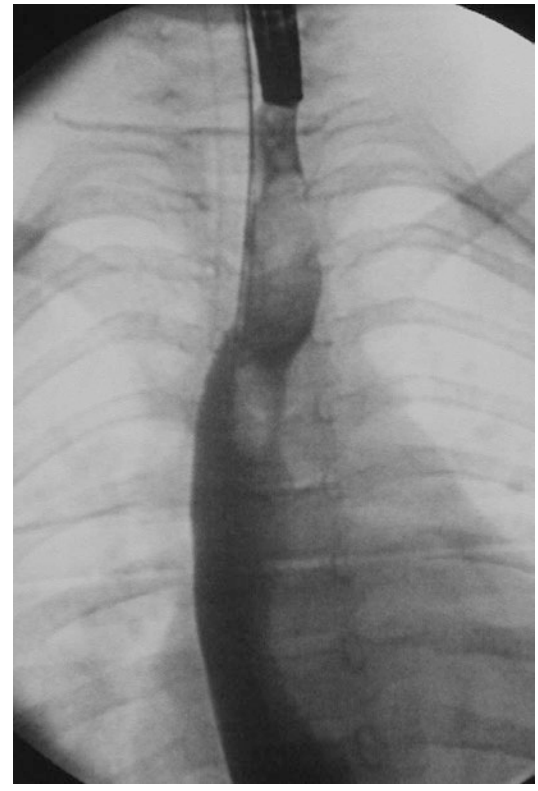

Fig. 38.3 Contrast and air are injected through the endoscope suction channel to rule out possible oesophageal perforation. Here a normal oesophagogram

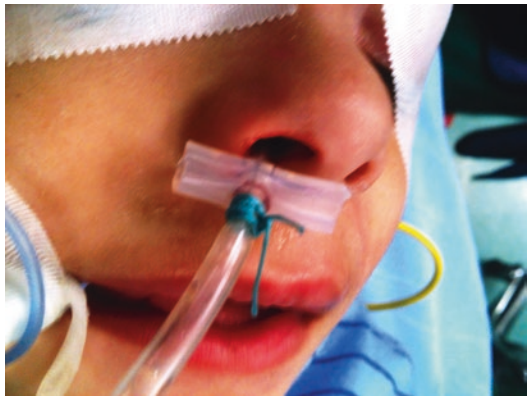

Fig. 38.4 The silicon bar affixed on the nasogastric tube, just outside the nostril, to avoid the distal stent dislocation

helping oesophageal plasticity and may therefore reduce scar development: the dynamic effect of this stent.

The stent is removed by the mouth after at least 40 days under general anaesthesia with endoscopic control of the oesophageal wall. In some cases, for logistical reasons, due to the distance from the hospital, the stent was removed later without complications. Extrapolating from the experiences of Attabek and Mutaf [8, 13], who left stents in place for 9–14 months, and our results showing a good stent tolerance, we now suggest leaving the stent in place for 2 months.

One month after stent removal, a barium swallow is performed to evaluate both the oesophageal lumen and the motility of the oesophageal wall. In case of partial stricture relapse it is likely to be less of a problem than before the stent treatment, and we advocate that the patient undergo monthly dilations. Gastro-oesophageal reflux disease (GORD) plays an important role in the scarring process and needs to be ruled out before considering a second stent. Reflux is often clinically not evident and Nissen fundoplication can positively change the patient clinical course. In case of early stricture relapse, especially if the stricture length is unaltered we would consider a surgical option rather than repeated dilations or a second stent. Psychological, social and logistical issues play an important role in this difficult choice and full counselling with the patient and parents is necessary. In case of recurrent strictures >2 cm in length, patients need a re-stenting procedure. Treatment is considered effective when patients are able to eat solid or semi-solid foods without dysphagia and when radiological studies show the resolution of the stricture.

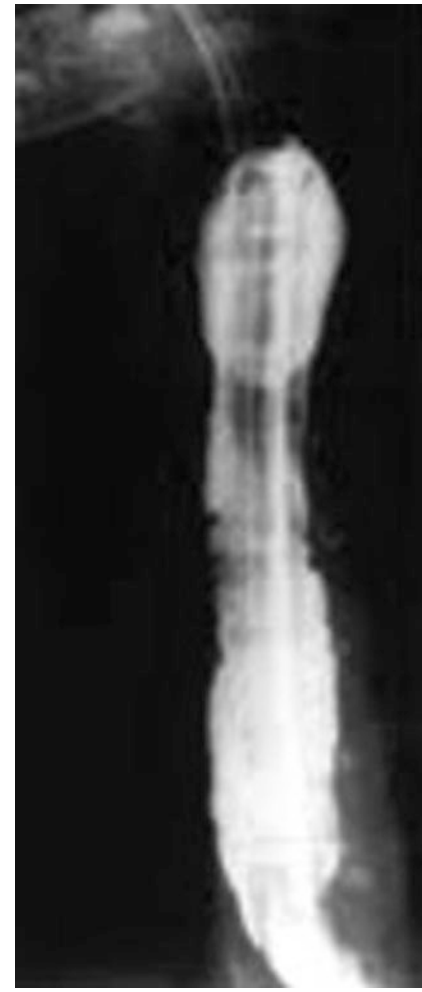

Fig. 38.5 The oesophagogram performed in the first day after stent insertion. The water-soluble contrast medium passes around the stent that appears in the correct position in relative to the cutaneous marks

During follow-up, all patients are investigated for GORD. For the first 5 years after stenting, patients have 24-h pH-monitoring sessions and oesophageal biopsies to rule out GORD and oesophageal dysplasia every 2 years. Subsequently, the patients will have examinations on the basis of clinical evolution, with

endoscopy and biopsies performed every 5 years at minimum.

Stent Indications

Following our results demonstrating a reduction in both the number of dilations and the duration of treatment [1, 8], in caustic OS, the dynamic stent represents our treatment of choice. In these patients, we insert the stent, if it is possible and safe, after the first dilation. In post-surgical OS, it is well known that only one or two dilations may be required to resolve the stricture and related symptoms and so we place the stent only after at least five dilations. In strictures that follow oesophageal atresia repair, before considering stent insertion, it is mandatory to rule out vascular anomalies, such as an aberrant right subclavian artery; vascular anomalies are not rare in oesophageal atresia patients. There have been reports of subclavian-oesophageal fistulas [14], with severe gastrointestinal bleeding, in patients treated with a stent and with an undetected vascular anomaly.

Results of Dynamic Stenting

In Table 38.1, we have summarized our experience in the treatment of OS with the dynamic stent: The mean length of the strictures was 5.4 cm (range, 1–11.5 cm). Forty (50.6 %) patients underwent several oesophageal dilations (mean, 5.1; range, 2–26) before stent placement. We performed 114 stent placement procedures in 91 patients. Stents were removed after a mean of 39 days (range, 15–65 days). In 80/91 patients (87.9 %), the custom stent was effective in achieving resolution of the stenosis and relief of dysphagia with normal food swallowing.

Table 38.1 Results of 91 oesophageal strictures treated with the dynamic stent from 1988 to 2012

Effective 80/91 (87.9 %)
Caustic 56/62 (90.3 %)
Post-anastomotic 21/26 (80.7 %)
Actinic 2/3 (66.6 %)
Ineffective 11/91 (12 %)
Caustic 5/62 (8.6 %)
Post-anastomotic5/26 (19.2 %)
Actinic 1/3 (33.3 %)

A total of 45/91 patients (49.4 %) received only one dilation contemporary to the stent placement and no post stent removal dilations. All of these patients were caustic, in many cases (24 %) previously treated with several dilations without clinical improvement at referral centres.

The custom stent was found to be ineffective in 11 patients (12 %): 5 with caustic strictures, 5 post-surgical strictures and 1 actinic stenosis. All of these patients successfully underwent surgical treatment, except two cases that only underwent dilations.

Of the 80 patients successfully treated with oesophageal stenting, 45 (56 %) did not require further dilations on long-term follow-up (median, 12 years and 4 months; range, 6 months to 24 years). In the other 35 patients, a mean of 6 dilations (median, 3; range, 1–33) were required after stent removal. Fourteen children (17 %) required more stents (mean, 2.7; range, 1–4) and dilations (median, 4.5; mean, 6.6; range 1–29) after stenting to achieve complete resolution of the strictures.

Eight patients were affected by double strictures, seven caustic ingestion cases and in one case of post-surgical stenosis. In all but one of these cases, complete resolution of the stenosis was achieved with the dynamic stent. In two patients, premature stent removal was required due to respiratory distress for acute reflux laryngitis in the pre-omeprazole era, and four subsequent dilations were necessary to obtain resolution of the stricture.

The oesophageal atresia anastomotic stricture group, from 1992 to 2012, comprised 387 patients (mean age 38.6 months; range: 3–125 months), some referred from other hospitals. A total of 1,583 endoscopic dilations were performed (mean, 4 dilations; range: 1–24). Oesophageal stenting was performed in 26 (6.7 %) of the 387 patients for failure of endoscopic treatment.

On follow-up of these anastomotic strictures, mean 5.4 years (range 6 months to 20 years) in

21/26 cases (80.7 %), the stent was effective with complete resolution of oesophageal stricture. In 5/26 (19.2 %) cases, a surgical procedure was necessary after stricture relapse. Stricture resection with jejunal interposition and oesophageal re-anastomosis were performed in one case and in four cases, respectively. In these patients, we obtained shortening of the stenotic area with the stent; therefore, in four out of five cases, it was possible to perform an easy oesophageal anastomosis after the stricture resection. Two patients (9.5 %) had severe dysphagia due to pronounced oesophageal dysmotility with consequent nutritional support through gastrostomy.

Severe symptomatic GORD represents an important problem in patients with OS. It was diagnosed in 15/26 (71.4 %), post-anastomotic strictures, in 14/62 (22.5 %) caustic strictures and in 1/3 actinic strictures; therefore, a Nissen fundoplication was performed.

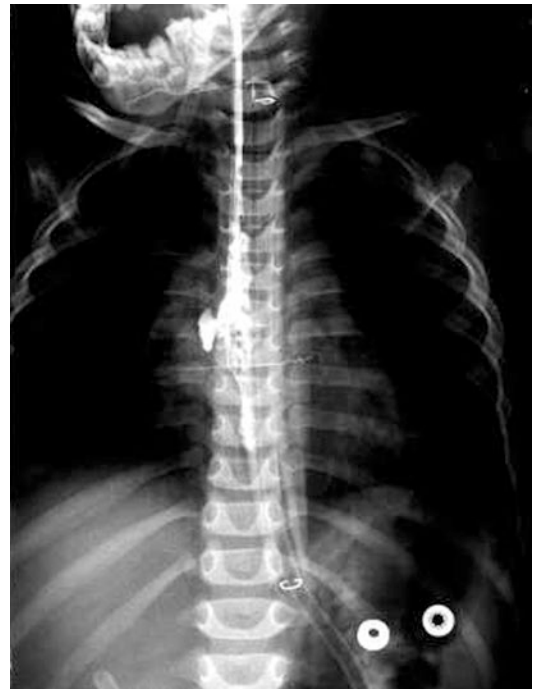

Fig. 38.6 This x-ray shows an oesophageal perforation with the stent in the correct position. The Replogle double-lumen suction 10 Fr drainage is at the perforation level for optimal suction

Complications

We observed two major complications being fistulas and perforation: subclavian-oesophageal fistulas with severe gastrointestinal bleeding in a patient with unknown aberrant right subclavian artery [14]. The patient underwent surgical correction with a patch repair and, after the second bleeding, with a graft substitution placing the graft anterior to the oesophagus.

Oesophageal perforation related to endoscopic dilation, which varied in severity, was observed in six patients. One patient died after incurring several systemic complications. In a second child, a percutaneous drainage of a mediastinal abscess was performed, and the stent was removed; after clinical resolution of this complication, the patient underwent a second stent with stricture healing. In a third child, a double-lumen 10 Fr suction tube was inserted in the oesophageal lumen alongside the stent at the level of the perforation, to obtain full suction (Fig. 38.6) with full recovery from the perforation. In the remaining three children, the minimal perforation spontaneously resolved with the stent in place. In patients with oesophageal perforation, dexamethasone therapy was started only after the perforation had sealed. Drooling and retching were always present on the first days after stent placement, but they resolved spontaneously, and all patients were able to resume a normal diet.

With respect to minor complications, we observed partial displacement of the stent in 15/114 (13 %) stent placements. In one case of proximal dislocation above the stricture due to post-operative retching, the stent was substituted with a longer one. In the other 14 cases of partial distal dislocation, due to food passage and incorrect fixation of the transverse silicone bar attached to the NGT outside the nose, the stent was correctly positioned again with simple traction on the NGT and the silicone bar was positioned more distally than before, thereby avoiding recurrence of this problem. In two more cases, the stent migrated into the stomach because of an incorrect stent fixation to the coaxial nasogastric tube. The stent was endoscopically recovered and substituted.

During the long-term follow-up, 30 patients (37.5 %) underwent Nissen fundoplication for severe GORD resistant to proton-pump inhibitors. None of the patients with endoscopic follow-up presented with oesophageal mucosal dysplasia or Barrett's oesophagus.

In summary, the dynamic stent represents an excellent alternative to tubular luminal stents and can reduce the morbidity from recurrent balloon dilations and potentially reduce the number of patients that need to go to surgery.

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Mitomycin C Application on Caustic Esophageal Strictures

39

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and Alaa Fayez Hamza

Introduction

Benign esophageal stricture in children is a common complication owing commonly to gastroesophageal reflux, esophageal surgery, and ingestion of corrosive agents [1]. Management of esophageal stricture is controversial between centers, and there is no standard protocol for management worldwide; however, it is almost agreed that endoscopic dilatation is the first line of treatment trying to preserve the native esophagus [2]. However, some cases are resistant to frequent endoscopic dilatation, and, therefore, another treatment modality is indicated such as esophageal stenting or surgical intervention. Among these strictures caustic one are the most difficult to be managed with high incidence of recurrence, and most of these children referred eventually for esophageal replacement procedure [2–5].

Background/History

Many researchers directed their effort to find adjuvant treatment to improve the results of endoscopic dilatation for resistant esophageal strictures. Several agents had been tried experimentally to inhibit new collagen formation and so preventing esophageal stricture recurrence, but none had been effective for clinical application [6].

Recently mitomycin C (MMC) – an antibiotic isolated from *Streptomyces caespitosus* that has significant antineoplastic and anti-fibrotic properties – was proved to reduce scar formation in animal studies [6]. Clinically, MMC started to be applied in many ophthalmological procedures, e.g., pterygium surgery and glaucoma and lacrimal duct surgery which proved to be effective in decreasing rate of recurrence and postoperative scarring [7, 8]. Then otolaryngologist started to apply MMC widely in their field that achieved good results in preventing recurrence when added to usual management of laryngotracheal stenosis, after surgical correction of choanal atresia and other different surgical procedures [8–11].

Experimentally mitomycin C application was effective in preventing strictures following caustic esophageal injury in rats in a duration and dose-dependent manner [6]. In the past few years, some case reports were published on the use of MMC topical application on esophageal strictures with promising results [12–16].

Evaluation/Indications

Management of esophageal strictures usually requires multiple endoscopic dilatation sessions for prolonged period of treatment reaching in

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some resistant cases up to 2 or 3 years. This long period of management and repeated dilatations have its psychological, social, and economic drawbacks on the child, parent, and medical society, and still there is high incidence of recurrence especially for those with caustic strictures [17, 18]. That is why the use of MMC as adjuvant to endoscopic dilatation could be of a great value as cost-effective modality in managing these patients.

Although MMC can adversely cause tissue sloughing and necrosis, bone marrow suppression, alopecia, nausea, and vomiting when administered intravenously or at high doses, topical applications in concentrations up to 0.4 mg/ml have been tried safely on esophageal strictures without local or systemic adverse effects with follow-up periods of up to 5 years [16].

Importantly, it must be emphasized that MMC has the theoretical risk of causing secondary malignancy in the long term [19]; however, in the early experience of MMC application in ophthalmological procedure, there were no malignancies had been reported in 870 pterygium cases in which MMC concentration of 0.4 mg/ml was applied and followed up for 10 years [7].

Treatment

MMC Dose and Concentration

Although the proper dose is not well studied yet, MMC concentration of 0.4 mg/ml that is to be applied topically on stricture site for 5 min shows to be effective and safe in short-term follow-up in our experience. Some authors reported the use of higher concentration up to 1 mg/ml without apparent side effect [12, 20]; however, further studies with long-term follow-up are needed to declare the most effective and safe concentration to be used on esophageal mucosa.

Application Technique

Topical MMC application is done after esophageal dilatation in the same session. The best is to apply the drug exactly on the area of denuded mucosa at stricture site after dilatation without touching normal adjacent mucosa with the applicator. There are many reported techniques for MMC application on esophageal wall; the classic first described one was by delivering a piece of gauze or cottonoid sponge soaked with MMC using a grasper forceps through rigid esophagoscope to the stricture site and to be applied sequentially on the four quadrant of the esophageal lumen. Although this way was easily practiced, it was difficult to control the precise application of the MMC to the site of the stricture only without unintentional exposure of normal esophageal mucosa to MMC, and also it was not applicable for long strictures.

At pediatric surgery department, Ain Shams University, Egypt, a modified technique was described using an applicator that was designed to match each stricture length individually for each patient. This was done using rigid esophagoscope and nelaton catheter as follow:

Nelaton Catheter Preparation

A nelaton catheter (size 10 FG) is prepared by wrapping a piece of cotton around its tip and circulating its terminal pores. This piece of cotton is secured in position using 3-0 silk suture; this fixation is done to secure the cotton piece from slippage during application. The length of the cotton piece is tailored according to the stricture length. Next, in vitro, the catheter is introduced inside the esophagoscope till the whole cotton wrap appears from its distal end, and then a mark is placed on the part of the catheter that just appears out from endoscope (catheter mark), to be sure during application that the whole cotton piece is applied on esophageal wall beyond the endoscopic distal end as the vision will be obscured by applicator during its introduction through rigid endoscopy.

Application Procedure

1. Esophageal dilatation – under general anesthesia and endotracheal intubation – using flexible endoscopy and wire-guided Savary-Gilliard dilators to appropriate size for each patient.
2. Reintroduction of flexible endoscope to accurately assess the site of the stricture (its distance from upper incisor) and its length in centimeter.

3. Marking the rigid esophagoscope with small adhesive tape at a point that is at equal distance to that measured by flexible endoscope corresponding to the site of beginning of the stricture (endoscopy mark). That is not to advance rigid endoscope beyond beginning of stricture which is more friable after dilatation to decrease incidence of perforation.
4. Introduction of rigid esophagoscope under vision till the endoscopy mark reaches the upper incisor. We confirm that we are at the beginning of the stricture by visualizing the denuded mucosa at stricture site after dilatation.
5. Introduction of the nelaton catheter inside the esophagoscope till the catheter mark is just at proximal end of esophagoscope. Now the cotton piece is just accurately applied on the stricture site.
6. Injection of 5 ml of the prepared MMC solution inside the lumen of nelaton catheter, that made the cotton piece soaked with the solution. This was left applied in place for 5 min.
7. Withdrawal of the catheter inside the esophagoscope not to expose proximal esophageal mucosa to MMC, followed by withdrawal of endoscopy.
8. Postoperative chest X-ray was done after complete recovery for exclusion of iatrogenic perforation.

Other authors reported different techniques by which MMC drug delivery was done through gastrostomy site with combined use of flexible endoscopy and/or fluoroscopy; however, it is to some extent a sophisticated technique, only applicable for patients with preexisting feeding gastrostomy, and it is hardly to be applied for long stricture [14–16].

Results

In pediatric surgery unit, Ain Shams University, MMC has been applied on caustic esophageal strictures of variable length on two clinical trials.

The first trial is a double-blinded randomized placebo-controlled trial on localized caustic esophageal strictures (<3 cm in length), wherein 40 patients were included in this study and were randomized into two groups, 20 patients in each group. Both groups were scheduled for regular endoscopic dilatations "session every 2 weeks for 3 months and then session every month for another 3 months"; assessment of stricture length was done in the first session, and MMC/placebo application was done in the second session, and subsequently the next scheduled sessions were done only if patient is symptomatic at its scheduled time. Assessment of patients after 6 months of drug/placebo application revealed that 16 out of 20 patients (80%) in MMC group had complete resolution of dysphagia after one session of MMC application and this raised to 18 patients (90%) after second application that was done after 6 months from first application, and this was compared with placebo group where only 7 out of 20 patients (35%) were resolved from dysphagia after 6 months of management. And it is remarkable that this significant difference in success rate between two groups was achieved with significant less mean number of dilatation sessions needed for MMC group (3.85) as compared to the placebo group (6.9). These patients are free of dysphagia for 9–36 months of follow-up with no recurrence.

The second trial was done on another group of patients (21 patients) with long caustic esophageal stricture (>3 cm and up to 8 cm in length) which resulted in resolution of dysphagia in 16 patients (76% success rate). Although these long strictures needed more dilatation sessions as compared to localized strictures and MMC was applied on multiple sessions (two to six times), however, these patients were previously referred for esophageal replacement due to failure of esophageal salvage by regular endoscopic dilatation.

Conclusion

According to these data, topical MMC application should be added to any standardized protocol for esophageal stricture management, as it markedly improves the response to endoscopic dilatation achieving a better quality of life for these

patients by preserving their native esophagus and decreasing the need for esophageal replacement procedures with its associated morbidities and mortalities.

Future Directions

Further studies are justified to investigate the proper dose and duration of MMC application as well as the number of application sessions that could be performed for each patient. Although this new treatment modality looks so promising in changing the quality of life for these patients with esophageal strictures, caution must be taken as regards its unjustified use as long-term adverse effect of topical MMC application on esophageal wall has not been studied yet.

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40 Reoperations After Esophageal Atresia Repair (for Significant Leaks, Recurrent Fistulas, Strictures, Residual Tracheal Pouches, Large Diverticula, Partially Intrathoracic Stomachs, and Failed Repairs)

John E. Foker

Introduction

Reoperation may be needed for a number of reasons following repair of esophageal atresia (EA) with or without a tracheoesophageal fistula (TEF). Although not all complications require reoperation, one may be desirable either because of the severity or to bring the problem to a close if nonoperative treatment has been unsuccessful. The judgments about the severity of the problem or the risk of reoperation will vary considerably among practitioners, consequently, so will treatment plans. For many surgeons, a reoperation understandably seems daunting and clearly requires experience and a center that is able to support complex procedures. Currently, there is a lack of clear definitions and guidelines for what deserves reoperation; nevertheless, with these variables in mind, we will present our approach for significant complications which we believe justify an operative solution.

Reoperation may solve the problem more quickly and effectively than other approaches, and this chapter will discuss why and how they are done. Among the significant complications of EA repair, the literature reports an anastomotic leak rate of up to 25% and a recurrent TEF (recTEF) incidence of up to 15% [1–6]. Postoperative anastomotic strictures are also common although the frequency has not been established because, to some degree, it is a subjective diagnosis without an agreed-upon definition. These problems as well as residual tracheal pouches, diverticula from a previous myotomy, and a partially intrathoracic stomach from whatever cause often deserve reoperation. The literature has shown that the significant early complications are more frequent in repairs of long-gap EA (LG-EA); however, even apparently successful short-gap repairs may have chronic problems worthy of reoperation [1–14].

From the literature, the majority of leaks apparently heal spontaneously, but some do not and may require reoperation to close a chronic lesion. A recTEF, in contrast, is unlikely to heal on its own because a mucosa-lined track usually forms which prevents spontaneous closure. Several endoscopic methods to treat a recTEF including stripping off the mucosa

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and/or plugging the track with various materials have been described [15]. Success, based on the patients referred to us, is unpredictable and the recTEFs often persist. Furthermore, a stricture in combination with either a leak or a recTEF presents an even more difficult problem because the usual methods of dilating the stricture will also likely keep either the anastomotic hole or the recTEF open. For these problems, reoperation will often be the best solution.

There are several other lesions following an EA repair which may be best treated by a reoperation. Occasionally, a residual pouch left in the tracheal membranous septum at the site of a lower segment fistula may enlarge, collecting mucous and bacteria which produce symptoms [12]. Although attempts to reduce the pouch have been made endoscopically, at present, a reoperation will likely be more successful [16].

Two other problems which result from techniques used to facilitate an anastomosis are a diverticulum from a circular myotomy or reflux from a partially intrathoracic stomach. Doing one or more myotomies or pulling the stomach part way up through the hiatus to allow a primary anastomosis in a longer-gap defect may have seemed like a good idea at the time; however, there may be unfavorable consequences. A myotomy may result in a large unsupported diverticulum which hinders food passage, continues to enlarge, and may even cause airway problems [13, 17]. For a partially intrathoracic stomach with the GE junction is in the chest, whether high or low, it is subjected to negative pressures, and significant reflux is predictable as are the consequences. These are difficult and reliably progressive problems which are very unlikely to be effectively treated without a corrective operation.

Most structural complications, with the exception of some anastomotic leaks, are unlikely to resolve without intervention and left untreated, usually produce significant symptoms. Consequently, for persistent problems resistant to nonoperative strategies, the indications for a reoperation will include large anastomotic leaks, recurrence of a TEF, a membranous tracheal pouch, significant GER, a recalcitrant stricture which does not relent with dilations and/or short-term stent placement, a large esophageal diverticulum, or a partially intrathoracic stomach. These are often complicated clinical situations and may require some combination of esophageal, tracheal, stomach, and diaphragm repair.

Reoperations, however, with predictable, often "dense" adhesions, the uncertain quality of the tissues to be repaired, and a lack of experience with difficult reoperations all may temper the surgeon's enthusiasm. The trepidation about reoperation may lead to a continued search for other solutions, to the detriment of the patient. Consequently, sending a patient with a significant chronic problem to a center where sufficient experience and expertise exists will make sense [11].

Reoperation, as a result, will fall to some surgeons, and the purpose of this chapter is to describe the surgical details which should aid in carrying out repeat thoracotomies with successful repair of the problems encountered.

The Surgical Technique for Reoperations

Timing of the Reoperation

The timing of the reoperation in relation to the previous thoracotomy or laparotomy will affect the ease of reentry. If the reoperation is done within about 10–12 days after the previous operation, reentry through the interspace and dissection throughout the pleural space will be relatively easy. Increasingly after this time and until at least 5–6 weeks later, the neovasculature that accompanies adhesion formation will insure blood loss during reoperation. After about 6 weeks' time, the vascularity will have largely regressed and, as the adhesions become filmy in nature, bleeding during reoperation will be less.

The Incision, the Interspace, and the Dissection

With the patient in a straight lateral position, perhaps tipped a little forward, the previous skin incision is usually reopened which will allow

access to virtually any interspace. Presumably, the original opening was correct for the initial lesion, and the recurrent problem will likely be in the same area and related to its repair. The same interspace is usually also reopened, but if one needs to be higher or lower inside the chest, a different interspace can be chosen. Admittedly, it will often be easier to enter through another interspace; however, the more interspaces entered, the greater the potential for fusion of multiple ribs, one of the causes of thoracic deformity [18].

A redo thoracotomy is more difficult for several reasons. Entering an interspace for the second or third time often means encountering fused ribs unless a piece of folded thin Silastic sheeting has been left between them. The rib fusion may be so dense that an osteotome will be required to separate them to gain entrance into the chest cavity. Only one corner of the osteotome should be used at a shallow angle to limit the depth of the cutting surface and avoid incising the adherent lung below.

Once the intercostal division is underway, the assistant elevates and pulls the ribs apart with two vein retractors, sturdy tissue hooks or similar instruments, creating a potential space which allows the lung to be dissected off the chest wall ahead of the osteotome. The dissection will be carried anteriorly and posteriorly in the line of incision and also superiorly and posteriorly to open the pleural space. The separation of the lung from the chest wall should be done as broadly as possible to avoid the disadvantages of working down in a tunnel. Elevating the rib cage, as described, makes the dissection easier, and at some point, a small chest retractor can be placed and it too can be elevated.

Carrying Out the Dissection

The general principle that will greatly aide achieving the preoperative goals will be to take down essentially all adhesions between the lung and the chest wall and, more posteriorly, with the esophagus. Depending on the location of the lesion and the size of the patient, it may not be necessary in a larger patient to take down all the adhesions medially between the lung and diaphragm.

The adhesions between the lung and parietal pleura are best taken down broadly and sharply under direct vision unless they are very filmy. The temptation will be to lyse as few adhesions as possible and go directly to the presumed site of the problem, whether it is esophageal or airway or both. This approach unfortunately results in a long, relatively narrow tunnel with the problem at the bottom. Effective repair, however, requires both good visualization of the lesion and mobility of the tissues to be brought together for closure. Consequently, dissecting the lung free and separating it from the esophagus will be important to success.

As noted, the dissection should proceed broadly anteriorly, superiorly, and inferiorly to prepare for the important posterior dissection. Then, lifting up the lung brings the dissection as much as possible up into the area of the incision and aids the lysis of the posterior adhesions by putting them on stretch. The lung can be elevated by using a small round peanut sponge held by a clamp, and, as the dissection progresses, a clamped larger tonsil or thumb sponge can be used to help separate the structures. In general, elevating the lung and bringing it and other structures up anteriorly rather than pushing them downward and medially will facilitate the dissection as it proceeds posteriorly. Elevation will create a potential space between structures which becomes realized as the dissection proceeds.

Completely freeing up these structures has at least two advantages. The nature of the problem will be better revealed, allowing lesions, such as fistulas to more remote parts of the bronchial tree, to be easily found. Secondly, and importantly, it will also provide the necessary mobility for effective esophageal and tracheal repairs. These repairs are much more difficult when the problem is seen at the bottom of a deep hole and hindered by the constraints of surrounding tissues and scarring. With experience, the dissection, which may seem daunting initially, becomes more straightforward and can be reliably done in reasonable time. This experience, nevertheless, will more likely be acquired at a center specializing in these problems.

Dissection of the Esophagus and Airway

With the lung essentially completely mobilized, it can be elevated and retracted medially revealing the esophagus and much of the posterior (membranous) aspect of the airway. The area of the anastomosis is usually the site of the problem whether it is a leak, a stricture, or the presence of a recTEF, and the dissection will be easier if this site is not approached first. A relatively normal portion of the esophagus, usually closer to the diaphragm, is chosen and dissected free (at least the anterior surface), and, if helpful, a loop is passed around it. The posterior and medial adhesions to the esophagus will also be put on stretch by the loop making them easier to divide. The looped esophagus is pulled toward the surgeon allowing its contour to be visualized and the surface followed precisely up to the problem area, avoiding a new injury to either esophagus or airway.

A fistula into the airway, whether proximal or distal, will become obvious by the air leak when it is divided. A recTEF in a larger patient may not require full mobilization of the esophagus if the communication is small; nevertheless, the entire anterior surface should be free for a tension-free closure of the esophageal end of the fistula. A stricture alone or in combination with a recTEF, however, will require complete and extensive mobilization of the esophagus to enable a well-constructed anastomosis to be created after the resection.

Nonoperative Closure of Anastomotic or Post-dilation Leaks

From literature reports, many esophageal leaks close spontaneously with adequate chest tube drainage, but sometimes they do not and a procedure may be required to close the hole and allow feeding to begin. Several endoscopic methods have been used and are usually the first approach if the hole is not large. The endoscopic results so far have been variable and success is generally inversely related to the size of the hole. As with any new technique, however, improvement can be expected.

Through the endoscope, the edges of the hole may be clipped together, and this is most likely to be successful if the hole is small or a vertical split as might occur after a dilation. Larger holes or those with edges that cannot be pulled together easily by clips will be unlikely to benefit from this technique and might be made worse by the effort.

Another endoscopic approach is the short-term placement of covered stents which allow closure to take place. Because these stents have had some success, they will likely be used increasingly in the future as more experience is gained. Stents also have the advantage of holding the lumen open while the hole closes and may limit the consequences of the stricturing tendency present early after completion of the anastomosis. A stricture may still form after stent removal, however, which poses a difficult problem because of the presence of the healed leak site with its potential for reopening if dilations are used. In this case, reoperation with the excision of both the stricture and leak site will be the best solution.

Finally, it has been claimed that a nasogastric tube can be placed down the esophagus and guided out the hole into the cavity providing a form of internal drainage. The abscess cavity may close down satisfactorily, which would allow the tube to be slowly withdrawn; nevertheless, this procedure would only be used in very unusual circumstances. No reports of the use of this technique have appeared in the pediatric literature.

In summary, each of these endoscopic techniques has succeeded and each has failed. Predictably with experience and better techniques, success will come more frequently; nevertheless, there will be leaks that require reoperation.

Suturing Techniques for Leaks or the Difficult Anastomosis

The repair of a leak will obviously be influenced by the size of the hole which will usually be either at the anastomotic site or a longitudinal split from dilation. With the lung mobilized and

retracted, the leak site will be exposed. An effective repair will require joining viable, full-thickness esophageal walls trimmed of any obviously infected, necrotic tissue. The suturing techniques will be similar to those used for a first time primary anastomosis. For larger holes, whose closure will be under tension, the intraoperative technique of gradually bringing the edges together to allow closure can be used. All the sutures for closure are accurately placed and tagged (Fig. 40.1). When all are placed, the sutures are crossed and used to gradually pull the edges together. When the edges are touching and held in position, individual sutures are tied off tension with the knots brought down carefully, keeping the edges in apposition.

Alignment of the esophageal wall edges to promote accurate healing is very important for successful closure of a hole or for the creation of an anastomosis. If the edges are not aligning well, then suturing techniques can be used to overcome the malalignment. Lembert-type stitches in which the very edge of the mucosa is caught by the suture will align the walls (Fig. 40.2). If one edge is turned up or down, angling of the needle as it passes through the wall will help correct this by lowering or raising the edge. The needle is held by a Castro-Vejho needle holder, which can be used like a pen to compose the anastomosis and make up for alignment deficiencies between the two ends. By angling the needle during placement of the stitch to include more outer wall and less mucosa will depress the edge of the esophagus (Fig. 40.3a, c). Similarly, angling the needle to include less wall near the outer surface and more on the mucosa side, it will elevate the cut edge of the esophagus (Fig. 40.3b, d). Careful sewing techniques such as these will align the edges of the esophagus for a successful closure of a defect or to produce a well-constructed anastomosis (Fig. 40.3c, d).

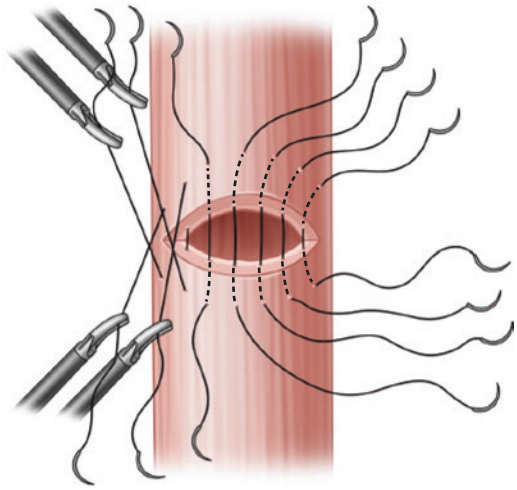

Fig. 40.1 Closure of an esophageal leak using preplaced, full-thickness sutures

The Recurrent Tracheoesophageal (Airway) Fistula

The literature indicates that in about 5–15 % of repaired EA cases, a fistula will later develop between the esophagus and the airway [1, 2, 4]. Most commonly, this is a recurrence of the original fistula between the lower esophageal segment and the back of the trachea or the proximal right main stem bronchus as found in the common form of EA (type C). Typically, recTEF becomes apparent within a few months of the original repair.

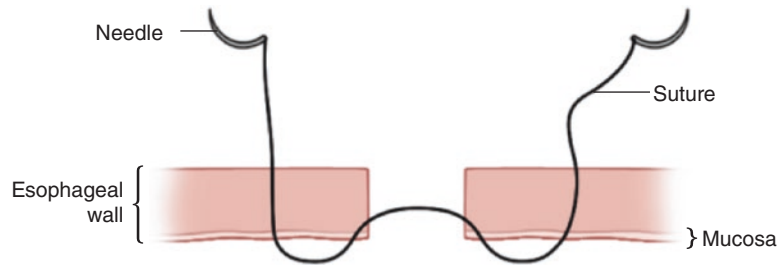

Fig. 40.2 Lembert stitch used to align the mucosal edges of the esophagus

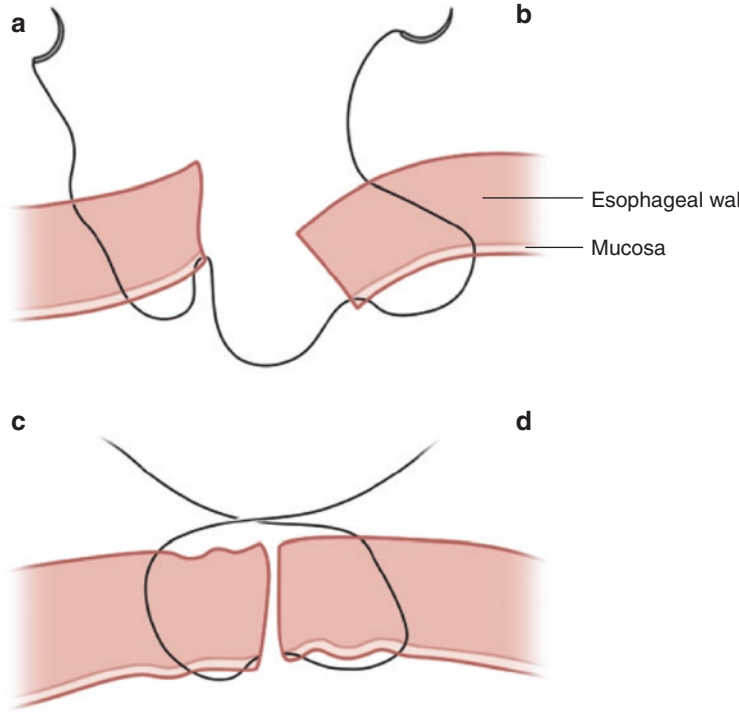

Fig. 40.3 Esophageal wall alignment disparity corrected by using angled needle and suture placement. (**a**) A wider tissue bite on the outer surface of the esophagus and narrow on the mucosal side will drop the edge and align as shown. (**b**) A narrower tissue bite on the outer wall and a wider bite at the mucosal side will elevate the cut edge. (**c**, **d**) When tied, the sutures placed as described above align the cut edges to promote accurate healing

The mechanism of recurrence presumably relates to the esophageal anastomotic line and the repair site of the airway being close together and vulnerable to the microabscesses which may appear in suture lines. An abscess will tend to migrate to a cavity, a lumen, or the outside. In the cases of the recTEF, the abscess migrated in order to drain, both into the trachea and back into the esophagus. Rarely, a similar inflammatory mechanism with a different location may result in the fistula entering the left main stem bronchus.

A recTEF is usually signaled by coughing, significant aspiration episodes, and pulmonary infections. In general, the more proximal and larger the TEF, the easier are the diagnosis and location established [4, 15, 19, 20]. The more distal recTEFs tend to be smaller and often require a careful contrast study to demonstrate a communication with the airway and provide an explanation for the pulmonary symptoms. The partial outlining of the distal trachea by an esophagram, done without spill over from above, satisfactorily confirms its presence and may identify the location. A fistula into a smaller bronchus can cause continued contamination of the airway; however, demonstrating it and localizing the site preoperatively can be difficult (Fig. 40.4). A small blush of contrast material from the esophagus into the lung field will establish the cause of the pulmonary

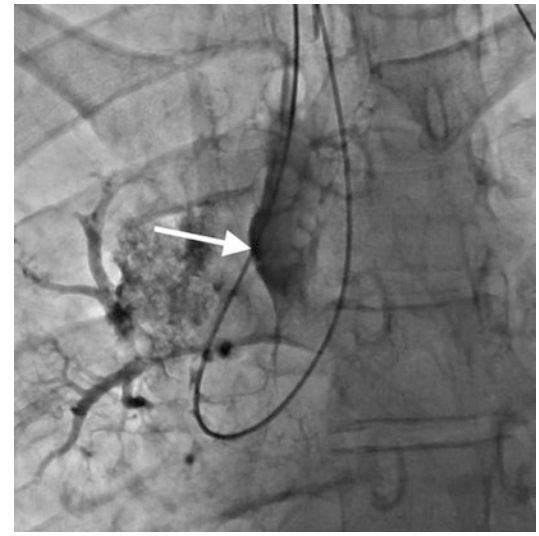

Fig. 40.4 X-ray showing a wire, which does not demonstrate the precise location of the airway entrance of a recurrent tracheoesophageal firstula (*arrow*)

problems, but may not provide much information on the location of the fistula into the airway.

When a fistula between the esophagus and airway is suggested because of the signs and symptoms and has been confirmed by a blush of contrast, the question becomes one of treatment. A recTEF, or even a de novo TEF, will pose problems and a conservative approach is unlikely to be effective [4, 19, 20]. The recTEF will soon be lined with mucosa which tends to preserve the lumen and prevent spontaneous closure. Furthermore, the presence of both a TEF and an accompanying stricture creates a difficult problem because adding dilations may also enlarge the TEF or at least keep it open.

The Later Appearing, More Remote Recurrent Tracheoesophageal Fistula

A smaller percentage of fistulas, however, occur at sites remote from the original TEF or develop following an EA repair even though none was present originally. The more distal airway fistulas may be less clear as to their cause, but likely began with a small abscess where the lung was adherent to the esophagus. Although the process may begin more peripherally near the surface of the lung, it can still find its way into a segmental bronchus and produce problems (Fig. 40.4).

In one case, a previously asymptomatic patient developed an occasional cough, not related to drinking liquids, 8 years after an uncomplicated repair of pure EA (type A). Contrast material injected into a small esophageal opening flowed through the peripheral lung parenchyma in an irregular path until it reached a small bronchus. The irregular path through the lung slowed the drainage of liquids; consequently her cough was sporadic and did not appear to be triggered by drinking.

Presumably, the recTEF began with the formation of an abscess in the peripheral part of the right lung which was adherent to the esophagus after the two earlier thoracotomies for the growth procedure. Again, the abscess migrated both to the esophagus and eventually to a small bronchus. Treatment required a reoperation with simple closure of the small esophageal opening and a more generous over sewing of the adherent pulmonary end. With a relatively small area of very chronic pneumonia adherent to the esophagus, it may be desirable to remove this portion of lung.

Nonoperative Methods to Close the Recurrent Fistula

The operative treatment of a recTEF may seem daunting because of predictable adhesions obliterating the pleural space and, often, because of its uncertain location. Consequently, a number of endoscopic methods have been devised to strip the mucosa and close the track, but these may not work and even might make the hole larger [15]. The methods range from laser treatments to plugging the fistula with artificial tissue membranes. More recently, tissue sealants in combination with the temporary placement of covered stents in the esophagus at the site of the fistula have achieved some successes with the more proximal recTEFs. The tissue sealants and implants do not seem to make the situation worse; however, they have not been reliable, are expensive, and may only delay resolution of the problem. Once the recTEF is established, the mucosa-lined fistulas resist closure and endoscopic procedures may not suffice for closure and reoperation will be necessary [15]. Other nonoperative methods of fistula closure will continue to be sought, however, and may, eventually, prove to be satisfactory and reliable.

Localization of the Fistula

If the fistula is a recurrence of the original TEF from the lower segment of esophagus (type C), its identification in the membranous portion of the trachea is reassuring as to where it will be at reoperation. For a fistula into the right main stem bronchus or even further out, the possibility of identifying and localizing it by bronchoscopy becomes progressively less even though the esophageal opening may be found. Because a TEF occasionally occurs more distally, it is

useful to understand how the TEF can be effectively located and treated despite the uncertainty and apparent difficulty it presents.

When the fistula can be visualized by bronchoscopy and an operative repair is planned, it has been frequently recommended that a catheter or wire be placed across the fistula to aid in locating it during the operative procedure [4, 19–23]. Although many surgeons have followed this advice which seems to have logic on its side, we have not found it either necessary or even helpful. The bronchial end of a distal fistula which is producing symptoms and problems, moreover, may be difficult to locate preoperatively by endoscopy causing consternation and even leading to the conclusion that "nothing more can be done." Beginning in Minnesota, where we were referred many recTEF cases and, more recently, in Boston where even a larger number have been treated, the operative approach to be described effectively revealed fistulas of any location and size without wire localization and allowed reliable closure.

Reoperation for Recurrent TEF

The operative approach is designed to insure the esophageal-airway fistula is found and divided no matter how small in size or distal in location. Once divided, this technique also maximizes the likelihood of a satisfactory repair with little chance of another recurrence. To accomplish these goals, the reoperation begins by opening the previous incision and dissecting the lung free, virtually to the diaphragm, so it can be elevated and the esophagus located. After the esophagus is first reached, usually well below the anastomotic site, the dissection follows the surface of the esophagus superiorly up into the thoracic inlet which will necessarily divide the recTEF. The separation of the lung and airway from the esophagus will efficiently reveal the divided fistula by the bubbling with ventilation at the site of the bronchial communication. Complete separation of the esophagus and the airway will also allow both ends of the fistula to be repaired under better visualization and, importantly, with less resulting tension imposed by inflexible, scarred surrounding structures.

The only fistula that could be missed by this technique would be in the cervical region; however, in this location, the preoperative studies would have identified it and the approach would be by a neck incision. And, although approaching a recTEF from the left side has been advocated, full mobilization of the structures would be made much more difficult by this approach which encounters the aorta [24].

The holes in a recTEF are typically small. A single generous, horizontal mattress suture should straddle the hole and incorporate almost the full wall up to the submucosa. When tied carefully, but not too tightly, the suture will provide a secure closure. A second more widely placed stitch can be used to reinforce closure but it must be tied even less tightly.

Another advantage of generous mobilization of the esophagus and tracheobronchial tree is that after the recTEF has been divided and repaired at each end, the two suture lines tend to lie some distance apart, further diminishing the chance of recurrence. If the two suture repairs remain close together, however, two or three relatively superficial sutures can be placed in the esophageal wall and posteriorly into the chest wall fascia to roll the esophageal closure further away from the tracheal repair.

As with the anastomosis, we believe the use of nonreactive sutures will minimize the inflammatory response. A simple repair using fine nonabsorbable monofilament sutures which are the least reactive material will minimize the occurrence of small abscesses. The choice between fine monofilament absorbable and nonabsorbable sutures will be made by the surgeon, but we have settled on the least reactive. Even absorbable sutures set up some local reaction with hydrolysis which helps make the case for a fine, nonabsorbable monofilament suture. Braided sutures are even more prone to microabscesses and silk sutures which are inherently very reactive would be the worst choice.

A 6-0 suture should be satisfactory for closure of the small fistulas. The knot should begin with two similar throws so it can be carefully tightened to bring the tissues together before a squaring throw locks it. The knot should be only

composed of four to five throws, and back pulling on the last throw will further lock the knot. The ends should be cut short to minimize the adverse effects of the suture material. These steps are done to minimize the occurrence of small abscesses which can enlarge and migrate toward the lumens of the trachea and esophagus, producing the dynamics which will result in a recTEF. This operative technique has been used successfully and without later recurrence in 38 consecutive cases in Minnesota and Boston where recTEF is a problem commonly referred for treatment [25].

A case has also been made in the literature for inserting tissue such as intercostal muscle or pleural or pericardial flaps between the suture lines to reduce the possibility of another recurrence. Again, although this may appear to be a helpful idea, the reported results seem no better than repairs without a flap and, compared to our experience, not as good [23, 26]. Any mobilization of flap tissue, moreover, may produce areas of necrosis and/or foster formation of microabscesses which add to the potential for a recTEF.

In summary, reoperation for a recTEF requires extensive mobilization and elevation of the lung and airway of the esophagus. This frees up a generous amount of the esophageal surface which will divide the connection and allows easy visualization of the holes, extensively mobilizing the esophageal wall so that an accurate and effective closure can be carried out. The tracheal repair should neither reduce the lumen size nor leave behind an unsupported pouch which may increase in size, harbor infection, and promote refistulization.

Strictures

As noted, clinical judgments about the severity of a stricture vary, but our definition has been that any visible anastomotic narrowing on a contrast study is at least a mild stricture. Even a mild stricture will likely produce some degree of dysphagia and perhaps episodes of food sticking. To function normally, the esophagus will need to be supple enough to allow the passage of solids of a larger diameter than the lumen collapsed at rest. Without distensibility, even a mild narrowing will limit the passage of some solids and be unpleasant for the patient. If a stricture is considered significant only when the lumen is clearly narrowed, patients with a lesser but real stricture will have to compensate by eating small bites of solids, with careful chewing to avoid food being caught at the site.

These two viewpoints are at the ends of a spectrum on how strictures are judged and treated. Because there is no agreed-upon definition of what constitutes a significant stricture, variation in the diagnoses and recommended treatments will continue to exist. The methods and vigor of the treatment will vary both from the judgments of the stricture and the experience and capability of those dealing with them. Mild strictures may not be addressed beyond the early postoperative period as the patients seem to be "doing well," and, as a probable consequence, dysphagia is very common even in adults who have had the common-type C EA/TEF repair in infancy [9, 10].

We believe a successful outcome of EA repair, however, does not include dysphagia, and these symptoms deserve evaluation and treatment. Dilations and, more recently, stent placement remain the first line of stricture treatment. The Minnesota experience has suggested relatively early, and frequent dilations seem more likely to encourage the stricturing tendency to relent rather than beginning dilations after more severe symptoms develop and the stricture is tighter [27, 28]. A more severe stricture will require more vigorous dilations, stirring up the mechanisms which lead to this problem.

Strictures, however defined, occur more commonly following repairs of longer-gap EA under tension and in patients with continuing gastroesophageal reflux (GER) [1, 2, 27–29]. The presence of GER will also be a persisting obstacle to effective stricture treatment, and, because late dysphagia is so common, the problem and treatment of strictures will be presented in detail.

Resection of Short Strictures

A variable of importance is the length of the stricture. Although most anastomotic strictures are relatively short and can be resected, the more recalcitrant ones may be relatively long making operative treatment including resection with primary anastomosis more difficult. For long strictures, the principle of growth induction by axial tension has been used to allow staged resection and eventual primary esophageal repair.

For relatively short, recalcitrant strictures, there are two operative options which preserve the esophagus. The first and most straightforward method is complete excision and reanastomosis. Even for a stricture length of 1.5 cm, however, complete excision will leave a gap of at least 4 cm after the ends retract, increasing the difficulty of the reanastomosis. This predictable situation is why surgeons may resort to a pull-up procedure for even a modest sized stricture. In experienced hands, however, resection and primary anastomosis keeping the GE junction below the diaphragm can be reliably accomplished and will prove to be increasingly beneficial over the succeeding years (Fig. 40.5a, b).

When making the decision to resect a stricture, several considerations should be kept in mind. The extent of the fibrous stricture may be longer than anticipated which, together with the retraction of for the divided esophagus, might make the resulting gap much longer than anticipated. The reoperation therefore should be approached in a flexible manner which does not prevent an eventual primary esophageal anastomosis and avoids a shift to a "rescue" gastric interposition. Finally, the entire stricture must eventually be resected; otherwise, the symptoms will persist and little will have been gained.

If there is uncertainty about the actual length of the stricture, the flexible approach would be to divide the esophagus in the center of the stricture and then systematically resect more until the surgeon believes that no more can be taken without

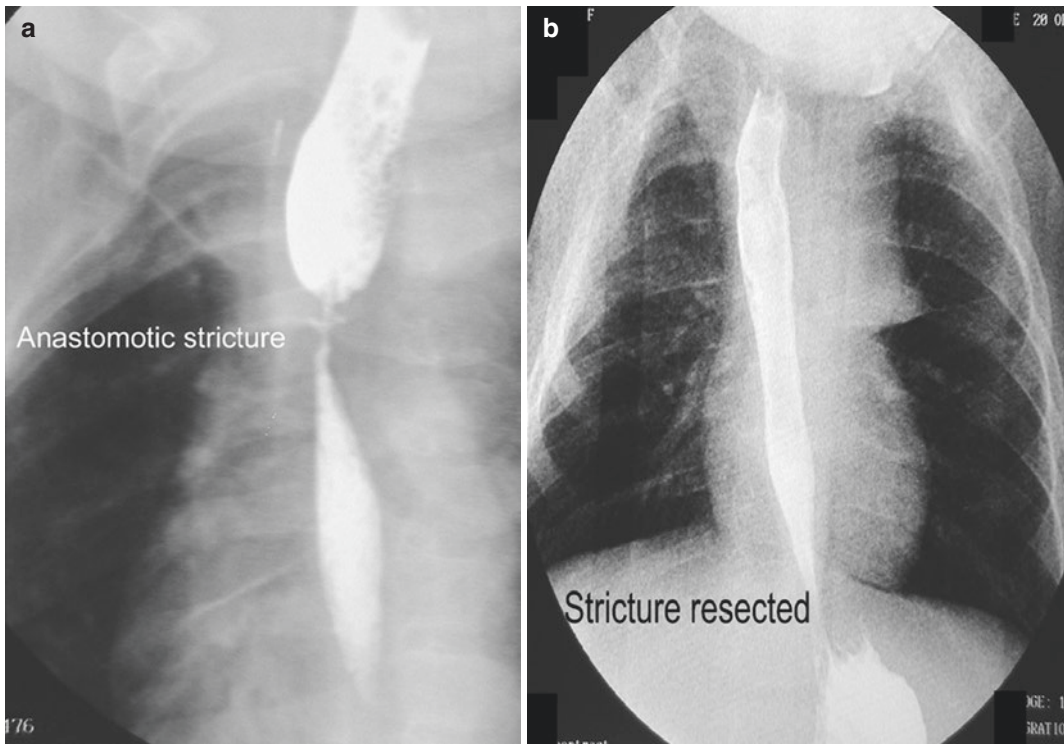

Fig. 40.5 Resection of a recalcitrant esophageal stricture. (**a**) Contrast study showing a 2 cm long anastomotic stricture. (**b**) Following complete resection and reanastomosis, the esophagus is of uniform caliber

jeopardizing the ability to accomplish an anastomosis. Once the esophagus has been divided and at least a portion of the stricture has been resected, there are three general possibilities for completion of the operation: (1) do a primary anastomosis even if the stricture has not been completely resected and plan on a second resection to remove the remainder in 7–10 days (2) close the ends or at least close the lower end and bring out a spit fistula, or (3) bring up an interposition graft. Only the first result, however, would be a completely acceptable outcome.

Resection of a stricture should be done carefully so that a primary anastomosis remains possible. A partial resection should be done initially and then more taken if an anastomosis under tension can still be accomplished. Sutures can be placed through the cut ends, tagged, and crossed to limit retraction. Under very special circumstances, the stricture can be 75–80% resected, leaving a strip of back wall, which will somewhat limit retraction and may add a sense of security. A complete resection of the stricture will be more desirable.

With more experience and careful attention to the details of creating an anastomosis, complete resection of a relatively short stricture will be reliably done. For longer strictures, a primary anastomosis will still be possible after using growth induction as part of a staged resection.

Stricturoplasty (Vertical Incision for a Short Stricture)

The second method, applicable for a relatively short lesion, consists of a longitudinal incision through the stricture with transverse closure. Although this will have the apparent advantage of largely eliminating the effect of retraction and preserving the back of the wall, it poses difficulties and leaves the original stricture in place, affecting perhaps 60–70% of the eventual circumference. To effectively relieve the stricture, the longitudinal incision must extend well above and below it; otherwise, even a transverse closure will not open up the lumen satisfactorily. It is the length of the vertical incision that determines how much the stricture will be opened. The upper and lower ends of the vertical incision will be brought together as the middle point of the transverse closure and consequently this distance may be much greater than the ends following a simple excision. The mid portion of the closure, therefore, may be under significant tension and difficult to bring together. This consideration limits this approach.

To accomplish this approach, after a suitably long opening has been made, closure begins by placing a suture at the midpoint on each side of the longitudinal incision. These sutures are tagged and pulled laterally to set up the transverse closure (Fig. 40.6a). Additional sutures to accomplish the transverse closure are placed, tagged, crossed, and put under increasing traction to bring the edges together. This method will be satisfactory if the mid-

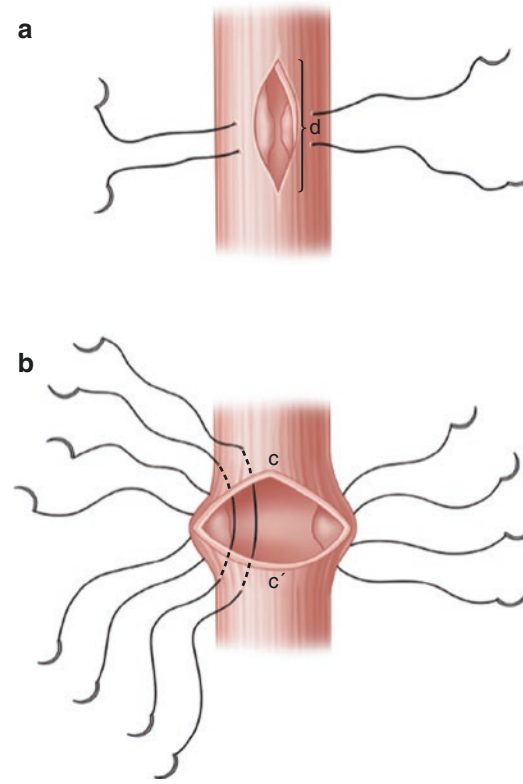

Fig. 40.6 A vertical stricturoplasty to treat an esophageal stricture. (**a**) A vertical incision divides the stricture. Midpoint sutures are placed to begin the horizontal closure. (**b**) Suture closure of the now horizontal opening. The upper and lower ends form the midpoint of the closure

points are not too far apart (Fig. 40.6b). Once the midpoints are essentially in apposition, the tying can proceed from laterally to medially on each end until the closure is complete. In this approach, a complete, full-thickness esophageal repair is desirable to avoid the use of a patch to complete the closure. The use of tissue patches to widen the lumen has been reported, and although colon patches will open up the area, their wall strength may not be adequate over the long term and a diverticulum may form [30]. Once formed, a diverticulum will have a tendency to enlarge, compounding the problem.

In summary, this technique of a longitudinal incision with transverse closure may appear useful under certain circumstances. In general, however, despite its initial appeal, it will only be workable for short strictures which are usually better served by resection.

Longitudinal Stricturoplasty

Another technique has been described which features a long incision through the fibrous portion of the stricture but only down to the mucosal layer [31]. The result resembles a pyloromyotomy for hypertrophic pyloric stenosis with mucosa bulging out between the edges of the split stricture. Given the probable need for a fundoplication and the sporadic contractile function of the lower esophagus following EA repair, the outpouching mucosa may begin to expand because of the slow emptying. Once the mucosa has begun to enlarge, the outpouching may continue to increase in size. Follow-up studies are not available in the literature; however, it does not seem likely that this method will provide a satisfactory long-term solution.

Residual Tracheal Pouch

If the tracheoesophageal fistula in the common form of EA (type C) is not repaired flush with the tracheal wall using tissue of good holding power, a pouch may develop. The pouch will tend to retain mucous and bacteria, leading to aspiration and other symptoms [12–16]. Although the natural history of these residual lesions from an EA/TEF repair is variable, because the pouches are relatively unsupported, they will often continue to enlarge, increasing the problem. Only local scarring associated with the original repair might impede this progression; consequently, when symptoms appear, the likelihood is that they will only increase in size and reoperation will eventually be needed.

To close the pouch, an essentially complete dissection is carried out and the lower trachea and esophagus separated. Because the wall of the diverticulum will be thin and easily entered, its location should be determined as the dissection proceeds superiorly. The light from a fine bronchoscope in the pouch usually provides the necessary information to safely continue the dissection upward.

Once the pouch has been dissected out and the esophagus retracted away, the decision on the specifics of the repair can be made. The repair will be carried out in a vertical direction and individual sutures on each side of the pouch should include a rim of the membranous septum. Although the membranous septum is relatively thin, the tissue is stronger than that of the residual pouch and a vertical closure will heal well and solve this problem. A vertical repair is desirable because the tracheal cartilages will prevent a horizontal closure of even a medium-sized defect.

The size of the pouch will affect the method of repair. If the pouch is small, endoscopic closure may suffice [16]. Larger pouches will likely require reoperation [12]. If the pouch is too big to be simply reefed up as the sutures are tied, it should be unroofed to leave less tissue folded into the closure itself; otherwise, later remodeling and regression of the wrapped up tissue might leave loose sutures and increase the potential for recurrence. There are no established guidelines; however, if the pouch is large and it appears too much tissue will be incorporated in the repair, a portion should be excised. These are the general principles; nevertheless, this repair is not without potential difficulties.

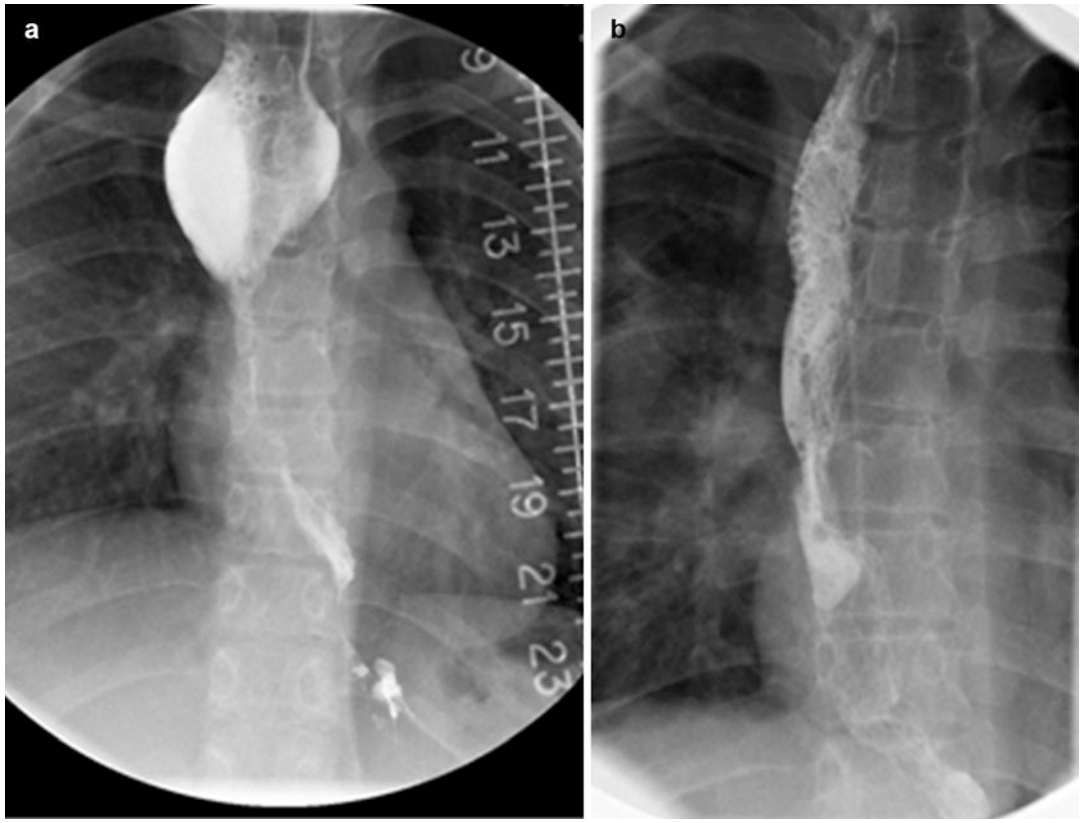

Fig. 40.7 Repair of an esophageal diverticulum. (**a**) Contrast study of an esophageal diverticulum. (**b**) Following esophageal growth and excision of diverticulum, a normal caliber esophagus was achieved

Esophageal Diverticulum

Following one or more circular myotomies, the unsupported mucosal wall of the esophagus will tend to enlarge, interfering with the esophageal emptying, and may even become a significant mass in the mediastinum impinging on the airway and causing ventilatory problems (Fig. 40.7a) [13, 17].

Repair requires reestablishment of a full-thickness esophageal wall; however, simple excision of a large diverticulum followed by anastomosis of the esophageal ends may be difficult. Given the tendency of the esophagus to retract, the excision of a 3–4 cm long diverticulum may result in a 6–8 cm gap between the esophageal ends and preclude an anastomosis. This variation of the long-gap problem can be remedied by first inducing growth of the esophagus above and below the diverticulum. Horizontal mattress sutures of 5-0 pledgeted Prolene are placed in the esophageal wall above and below the diverticulum, crossed and anchored either into the paraspinal ligaments or into the chest wall on the other side of the diverticulum. When these sutures are tied, the diverticulum will collapse and the normal esophagus will be stimulated to grow (Fig. 40.8). This approach uses the basic principles of axial tension to stimulate growth combined with not entering the esophageal lumen until one is ready for a primary anastomosis. After 5–7 days of this form of internal traction, a primary esophageal anastomosis will be much easier to achieve (Fig. 40.7b).

When the upper and lower portions of the esophagus are sufficiently close for a full-thickness anastomosis, then the diverticulum can be treated in one of two general ways. If the diverticulum was large, it is better excised. Generous suture

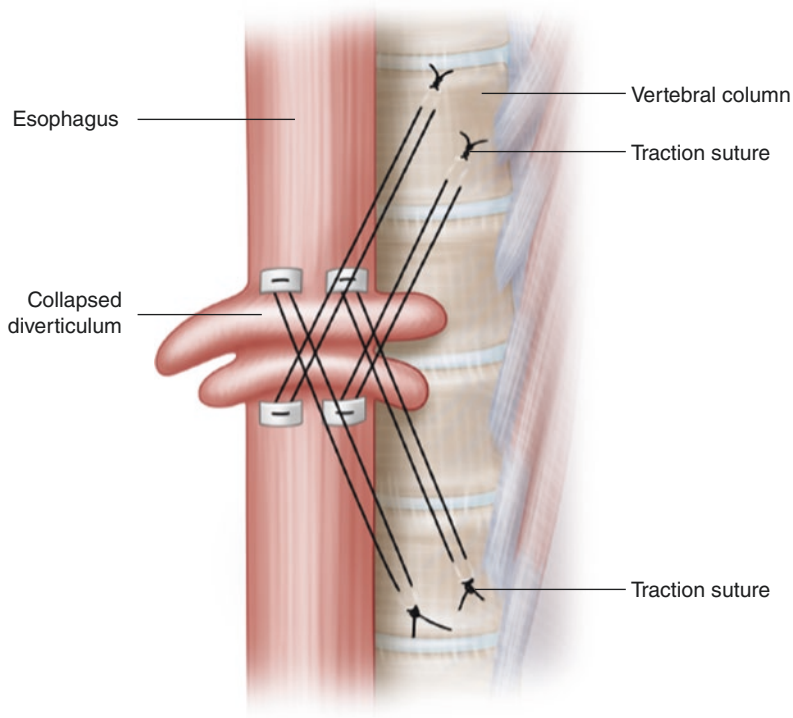

Fig. 40.8 Diagram of a diverticulum collapsed by sutures with resulting axial tension on the normal upper and lower esophagus inducing growth

bites are taken for the reanastomosis and placed in a Lembert fashion to bring the mucosal edges together (Figs. 40.2 and 40.3). In some cases of a relatively small diverticulum, however, the mucosa may be imbricated carefully with the sutures not entering the lumen. In this situation, the mucosal folds, if relatively small, can be expected to remodel and regress. The holding power will come from generous tissue bites in the esophageal wall as in any anastomosis.

By using one of these methods, a very satisfactory repair can be achieved. This overall approach will have the substantial long-term benefit of avoiding an interposition graft.

The Partially Intrathoracic Stomach

Whether by design to allow a primary anastomosis, or as a consequence of a large esophageal hiatus, from the result of traction sutures used to induce lower esophageal growth or from an esophageal anastomosis under significant tension, the GE junction and part of the stomach may be above the diaphragm. This configuration is detrimental for the long term because it insures GE reflux with its long-term adverse consequences. For the short term which may be 1 or even 5 or even 10 years, this problem may be treated in a symptomatic degree by antacid therapy; nevertheless, the effects of chronic bile reflux will prove to be increasingly detrimental, making unlikely the goal of 70 good years [31]. This unsatisfactory sequence of events will likely also be seen following gastric pull-up procedures, but the return to the abdomen in these cases will require a jejunal interposition to restore continuity.

The difficulty in correcting the partially intrathoracic stomach will be in rough proportion to how much is above the diaphragm. If the stomach has been brought up through the hiatus to allow an esophageal anastomosis, a significant amount may be in the chest. Even an unplanned hiatal hernia, however, may be relatively large and pose problems. Anatomic and physiologic correction

will require bringing the GE junction at least 2 cm below the diaphragm, and the esophagus will likely be "too short" for this to be easily accomplished causing a similar deficiency problem as found in long-gap EA.

Two methods have been used by us to return the GE junction below the diaphragm. The first is relatively straightforward and consists of full mobilization of the esophagus and placing a 3-0 monofilament suture superficially around the GE junction. The GE junction can usually be identified by surface characteristics of the esophagus in contrast to the stomach, as well as the presence of a branch from the vagus nerve which crosses the GE junction transversely along with a vein. This localization is important so that the subsequent wrap is around the esophagus and not the upper stomach. With downward traction on the 3-0 Prolene suture, and continued freeing up of the esophagus as it is pulled downward, the GE junction may be brought far enough below the diaphragm to allow a proper fundoplication to be done (Fig. 40.9). After reducing the hiatal opening and completing the wrap, the 3-0 Prolene suture is removed.

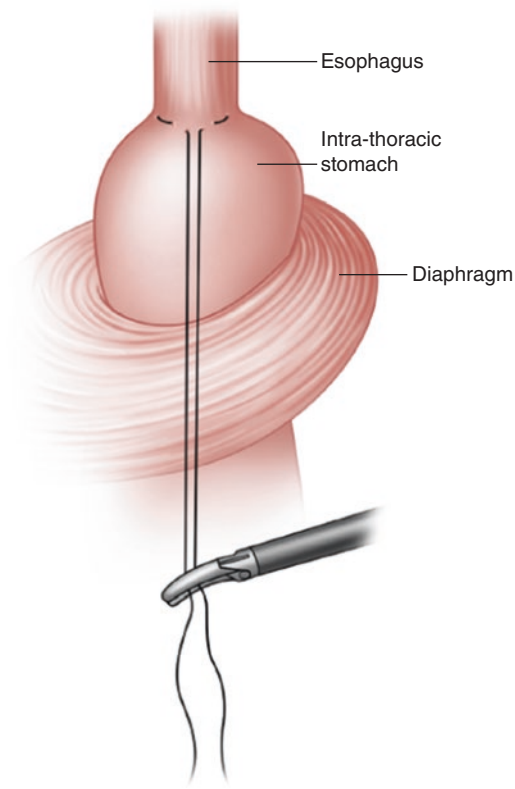

Fig. 40.9 Diagram of pulling down an intrathoracic stomach

Sufficient mobilization of the esophagus may also require reopening the thoracotomy incision and, although this increases the magnitude of the operation, we believe that a partially intrathoracic stomach is so detrimental over the decades that the combined incisions are more than justified to return the GE junction to the abdomen where it belongs.

The second method has not been described to our knowledge and may seem to be unorthodox; however, it is relatively straightforward and effective. This technique can be successfully used when the GE junction cannot otherwise be brought below the diaphragm.

The concept is simple enough. If the GE junction can't be brought below the diaphragm, the diaphragm can be moved above the GE junction (Fig. 40.10). Normally, the diaphragm dips downward posteriorly with the esophageal hiatus located well below the apex. The diaphragm can be detached along its posterior aspect, and when a sufficient length has been freed-up, it is anchored higher on the chest wall, well above the GE junction with nonabsorbable pledgeted horizontal mattress sutures (usually 4-0 Tevdek). The edge of the diaphragm will need to be split at an angle for a short distance which will place a strip of muscle between the esophagus and the posterior chest wall. The diaphragm will be closed around the esophagus to fashion a new hiatus. The innervation of the diaphragm is from the phrenic nerve which fans out from its central location; therefore, detaching the diaphragm posteriorly will not interfere with function.

This operative maneuver is not difficult, and small, posterior remnants of the crura may be left behind in the abdomen which will indicate the previous location of the esophageal hiatus. With the diaphragmatic opening higher on the esophagus, a fundoplication can be carried out in the usual fashion with the wrap and GE junction within the abdomen (Fig. 40.10).

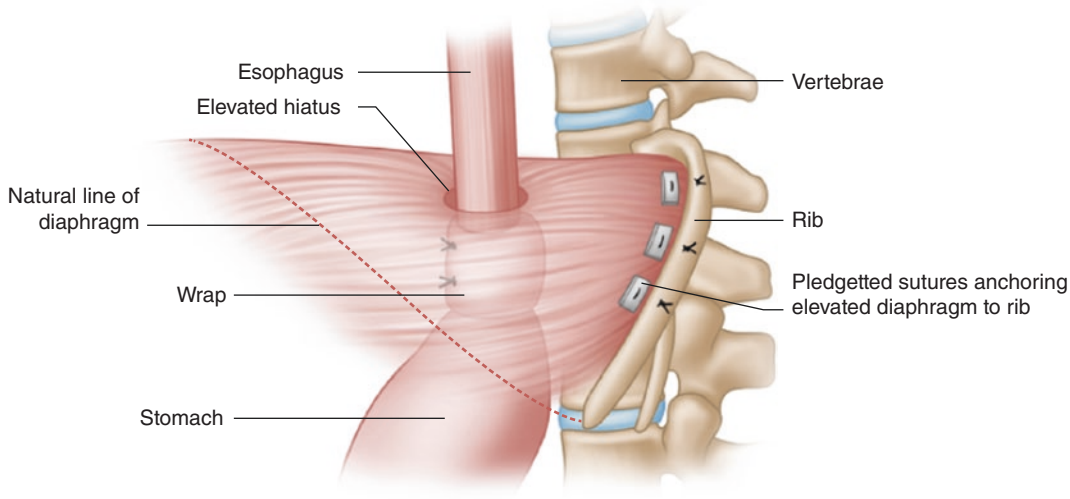

Fig. 40.10 Diagram of moving the diaphragm upward

In contrast to these methods, a partially intrathoracic stomach is in adults commonly treated by a Collis procedure in which the upper stomach is cut downward in the line of the esophagus and the resulting piece of greater curvature used to complete a type of fundoplication below the diaphragm. Obviously, this leaves the true GE junction in the chest along with the length of stomach which remains above the fundoplication. Although this may seem to provide a solution, the presence of gastric mucosa in the chest and the frequent lack of an effective pressure zone producing a physiological GE junction means acid production and reflux will continue to occur. For the long term, this situation will likely be very detrimental, and even the short-term results have been unsatisfactory [32].

Growth Procedure Following Previous Attempts at Repair of Esophageal Atresia

A patient who has had a failed EA repair which has included several operations may have little remaining esophagus. The choice will be between an interposition graft and a growth procedure. Although the prospect for a growth procedure can be daunting, it may still be possible to locate sufficient esophagus to produce an effective growth response, leading to a primary repair with the GE junction below the diaphragm. In such a case, the less desirable interposition may be avoided (Fig. 40.11a, b).

Summary

Reoperation, as discussed in this chapter, may be the best solution to a difficult and persistent problem. Avoiding a reoperation may have its appeal, but postponing effective treatment in these situations may be quite detrimental to the patient. The technical details for the successful treatment of several problems are presented, and, where a significant esophageal gap may result from the procedure, the methods to induce sufficient growth are also discussed. Reoperation, however, requires experience and may be best undertaken at a suitable center, where the approach can be adequately carried out.

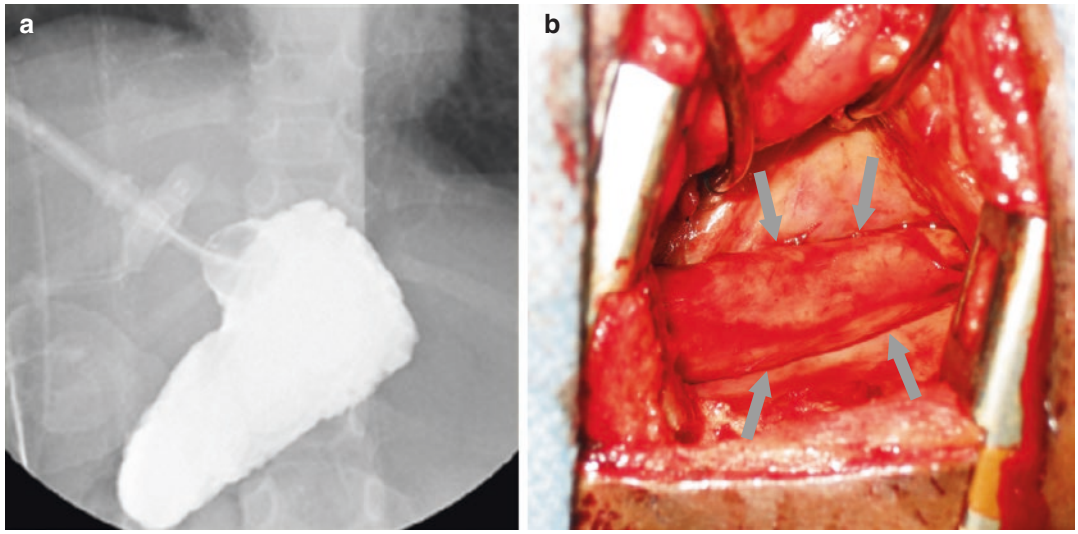

Fig. 40.11 Growth procedure following multiple operations for EA: (**a**) gastric contrast study of a 2-year-old who after eight operations, including cervical esophagostomy revisions, appeared to have completely lost her lower esophagus. The gap length to the upper pouch was 16.5 cm. (**b**) At laparotomy, a nubbin of the esophagus was found, and by axial tension, a very satisfactory lower esophagus was grown. The *arrows* indicate the edges of the new lower esophagus. After a primary esophageal repair, she eats normally

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Growth Induction to Treat Long Esophageal Strictures

41

Tara C. Kendall Krosch and John E. Foker

Introduction

Esophageal strictures are a frequent consequence of the repair of esophageal atresia (EA), especially in the case of long-gap EA (LGEA). The principal method of treatment has been esophageal dilation, previously with rigid dilators, but now balloon catheters are commonly used [1–8]. More recently, removable stents and injections with mitomycin C or steroids have also been used to inhibit stricture recurrence, but the rate of their successes in children has not yet been determined [9–14]. Despite treatment which may include frequent dilations, injections, and removable stent placement, in some patients significant complications occur or the stricturing tendency remains active with continuing dysphagia [15–17].

Resection of the stricture followed by primary anastomosis of the normal esophageal tissues could solve the problem and provide the greatest benefit. The difficulties of this procedure, however, are well known and begin with a redo thoracotomy and takedown of extensive adhesions (see Chap. 40: "The Redo Operation"). A stricture, moreover, does not end sharply and typically tapers; therefore, a complete resection usually must extend further than expected. In addition, once resected, the esophageal ends will retract, making the resulting gap much longer than anticipated and the repair daunting.

Stricture resections, nevertheless, have been attempted, and the resulting dismaying gaps have led to additional maneuvers to make an anastomosis possible. Esophageal myotomies have been used or part of the stomach has been brought up into the chest to close the gap and allow an anastomosis. An alternative approach has been to incise the stricture longitudinally; however, the longer the lesion the less likely the obstructive effects will be relieved. Because of the anticipated difficulties, long strictures have often led directly to interposition grafts, typically of the stomach or colon, to bridge the gap after resection. These solutions, however, all have drawbacks which tend to increase with time. Because of these significant shortcomings, we have used growth induction to treat long, resistant strictures and end up with the long-term benefits of a true primary repair.

Principle of the Procedure

The basic principle of treating long strictures by resection is the same as for primary repair of LGEA; tension is created to provide the growth signal in the normal portions of the esophagus.

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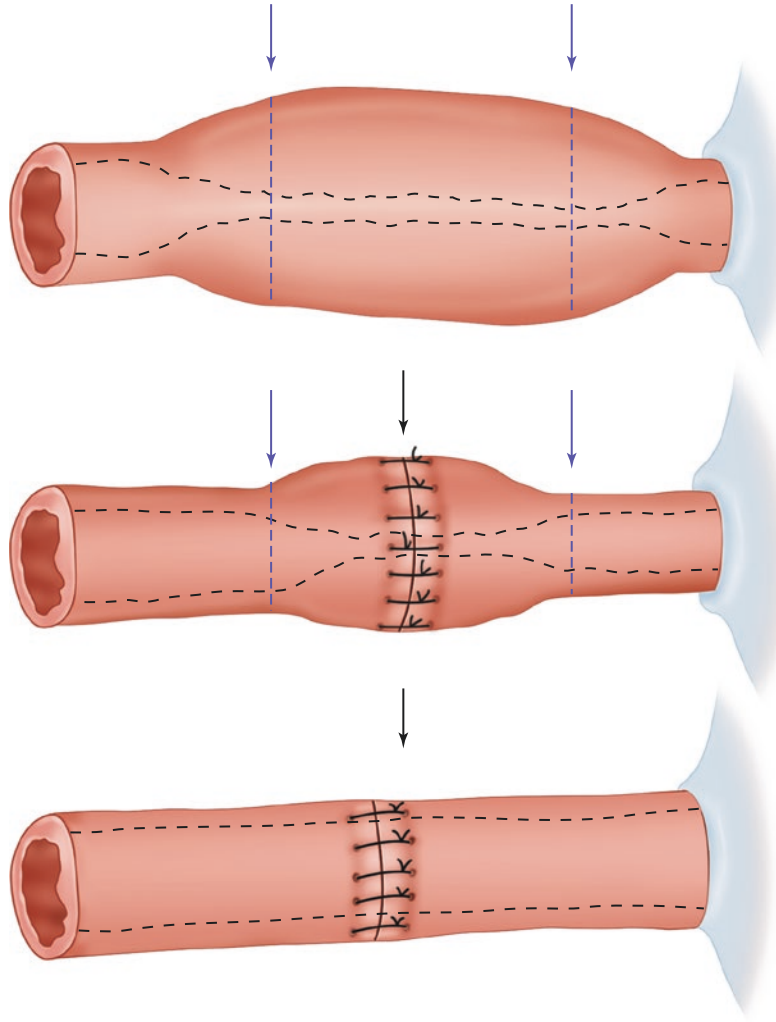

Fig. 41.1 Diagrammatic representation of a staged resection of a long esophageal stricture, in this case, a fibromuscular stenosis (see also Fig. 41.2). The resection begins in the middle of the stricture. A sufficient amount is removed so the resulting anastomosis will be under moderately severe tension which will induce the normal portions of the esophagus to grow. About 7–9 days later, another resection is done and, in this illustration, the remainder of the stricture is removed. We have used up to four resections to remove a long (12.5 cm) stricture. Although a well-constructed anastomosis is required, the tension reliably induces growth of the normal esophagus and will fill the gap caused by the resection

When the growth response is sufficient, a true primary repair becomes possible using only native esophagus. The difference between the two situations is that by resecting the stricture, a long gap is created, while for the LGEA lesions, it already exists. The growth signal, however, is basically the same although it is renewed in different ways to produce sufficient growth to bridge a long gap.

For a stricture too long to be completely excised and still allowing a true primary anastomosis, growth is induced by resecting it in stages. A section is removed from the middle of the stricture which leaves a long but manageable gap and two open esophageal ends. The new anastomosis will necessarily be under tension which provides the growth signal to the esophagus above and below the stricture (Fig. 41.1).

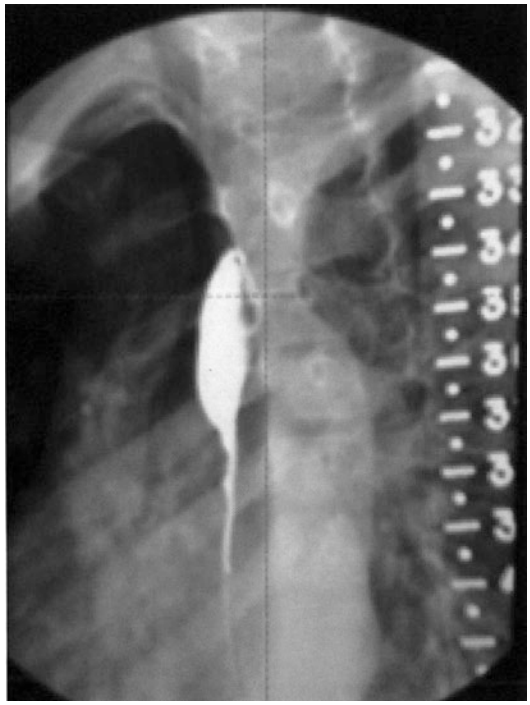

Fig. 41.2 Radiograph of a 6-year-old male with a long congenital (fibromuscular hypertrophy) stricture. He had never eaten solid foods and even the swallowing of liquids was a laborious process. Although three resections were used to completely remove the 6.5 cm stricture, two might have been sufficient. The first two resections were done only 3 days apart, and there had been insufficient time to maximize the growth response; therefore, the second resection was smaller

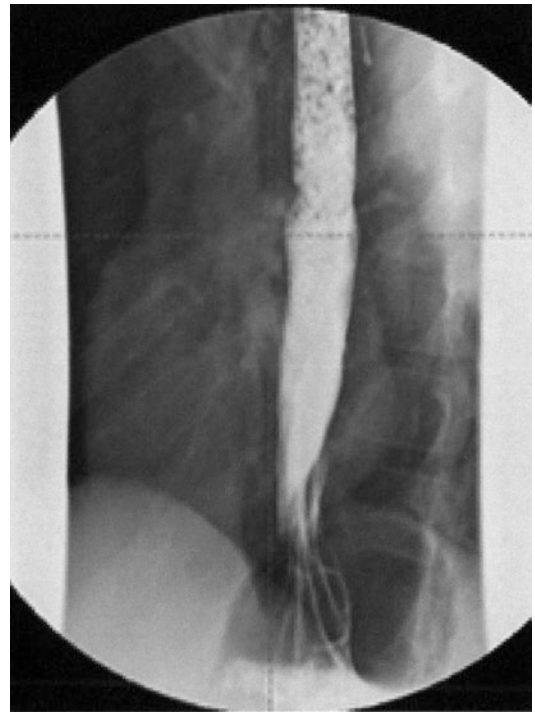

Fig. 41.3 After three resections of the fibromuscular stenosis, complete excision was achieved and the resulting esophagram was quite satisfactory. The patient is in boarding school and now eats the standard meals without difficulty or symptoms of dysphagia

This approach, however, requires a well-constructed esophageal anastomosis that will withstand significant tension and provide the axial force which will induce growth in the normal portions of the esophagus. By proceeding in stages, even long strictures can be successfully resected, leaving an intact esophagus with the GE junction below the diaphragm. A staged stricture resection, therefore, will solve the problems often associated with other methods to relieve a longer stricture. Even though this approach seems formidable, in practice it is straightforward, and the relief of a resistant and troublesome stricture pays considerable long-term benefits. Rather than being a solution that likely will deteriorate with time, it should be durable if the predictable postoperative issues, especially gastroesophageal reflux (GER), are also effectively treated (Figs. 41.2, 41.3, 41.4, and 41.5).

The Staged Operative Approach for Long Strictures

Through a posterior-lateral thoracotomy, which will usually be a reopening of a previous incision, the lung is dissected free and the esophagus mobilized completely (see Chap. 40: "The Redo Operation"). Once the esophagus is freed up, the stricture should be apparent although sometimes it is not, and a large red rubber tube or an endoscope passed from above will be helpful in finding it.

At the first operation, the surgeon should remove as much stricture as felt to be consistent with being able to create a primary anastomosis, necessarily under tension. The first operation will

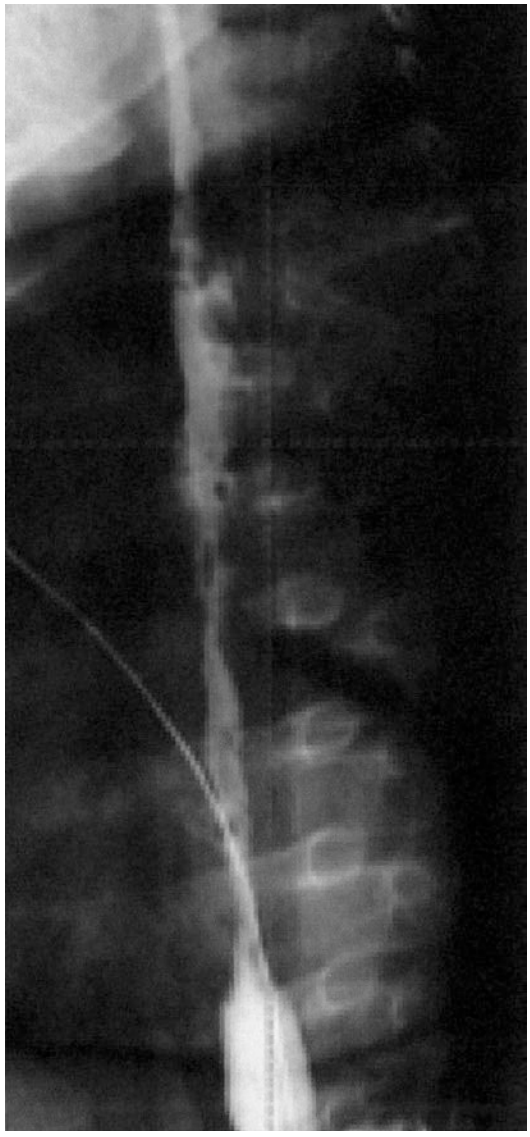

Fig. 41.4 An esophagram of this 2.5-year-old male shows a long (12.5 cm) and very tight stricture after ingesting lye in his home country 5 months earlier. The contrast study also shows a very short distal segment of normal appearing esophagus entering the stomach. A similar length was present proximally in the cervical esophagus, although not seen on this frame. Multiple dilations had been carried out with no result except a perforation and significant mediastinitis. After arrival in Minnesota, the choice presented was between a staged resection and an interposition graft (jejunum), and the former was chosen. Very helpful to accomplishing a staged resection was the very thick wall of the stricture area. Despite the obvious inflammation, loss of the mucosal layer, and breakdown of the normal esophageal wall structure, the tissue strength was more than adequate to allow an anastomosis under significant tension. Although the mucosa had been largely destroyed, and the lumen very narrow, it was sufficient to allow the passage of saliva which made the time between resections tolerable

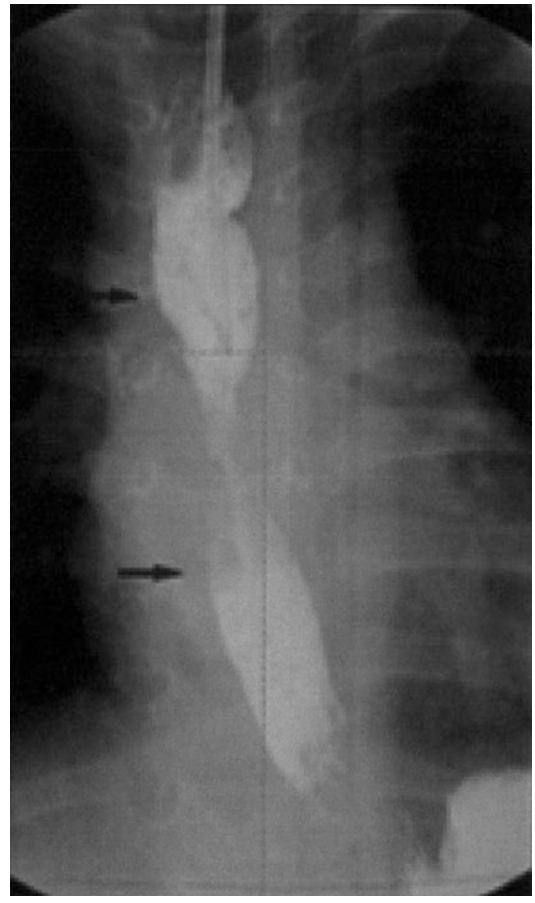

Fig. 41.5 After two resections, an esophagram showed a much shorter but still substantial area of stricture (*arrow*). The length of normal esophagus above and below the stricture has obviously grown considerably

require judgment because with retraction, the gap will become longer, and if too much is taken, the anastomosis may not seem possible and this approach will be abandoned.

The tension of the anastomosis provides a single stimulus which dissipates as growth occurs over the next several days. After about 7–9 days, essentially all the tension-induced growth will have taken place and another partial resection and anastomosis can be carried out. Within this time frame, vascular adhesions will not have formed and the repeat thoracotomies will not be difficult. Re-resections are approached through the same incision, and reentry can be made easier with the placement of very thin silastic sheeting in the rib interspace after each operation. Our practice is to not pull the ribs tightly together with pericostal sutures which

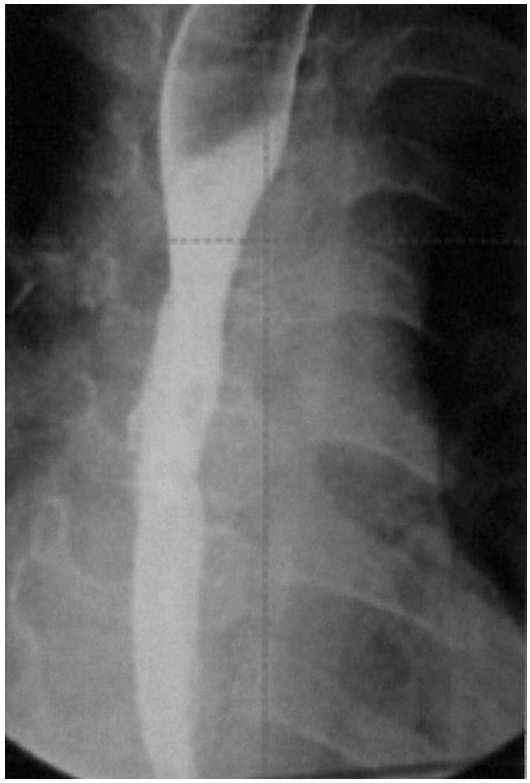

Fig. 41.6 After two more resections, the esophagram looked essentially normal, and following a fundoplication, he began a normal diet for the first time. The follow-up history is noteworthy. He and his father wished to return home after the last resection and before the dilations were completed. Consequently, he developed a short but resistant stricture and about 1 year later returned to Minnesota where the stricture was resected. After three dilations, he returned home where his subsequent course has been excellent. Follow-up endoscopy at age 15 revealed a normal appearing esophagus. Recently he has entered the KSA Air Force Fighter Pilot Training Program, something which would have not been possible with a colon or stomach interposition graft. Although this approach required several operations, the outcome has been excellent as is the long-term outlook

leaves a normal intercostal space and helps prevent fusion of the ribs. The number of resections required to remove the entire stricture will depend on its length and the experience of the surgeon.

At each stage the middle portion of the stricture is resected (Fig. 41.6). The amount removed will be decided by the surgeon, but, in general, after a 2–3 cm resection, retraction will result in a 4–5 cm gap, and a primary anastomosis will be under moderately severe tension. The technical details of completing an anastomosis under tension have previously been described (Chap. 25: "Growth Induction and the Flexible Approach"). Briefly, the back rows of sutures are placed taking generous tissue bites and then individually tagged. The sutures are crossed and, with continuous traction, the esophageal ends are slowly brought together. Because the anastomosis will be under tension and the esophagus not easy to turn, the back row will be tied on the inside. While maintaining tension on the crossed, untied sutures, one suture pair is selected and tied off tension which should prevent it from pulling through the tissues. When tying, the first two throws are not squared so the knot can be cinched down carefully to just bring the tissues into apposition without making the suture too tight and causing necrosis. The third throw is squared which will lock the knot. The suture material we use is typically 5-0 monofilament polypropylene, chosen because of its nonreactivity and its ability to slide easily through the tissues.

Treatment After the Last Resection

Fibroblasts produce anastomotic healing, and therefore, some degree of contraction occurs naturally at the circular repair site. This tendency will be increased by anastomotic tension and GER, both very likely to be present. Once the resections have been completed, a contrast esophagram is done 2–3 weeks later followed by evaluation with endoscopy. Evaluation for GER at about the same time has also been part of the treatment plan, and often, a fundoplication will be necessary.

Esophageal dilations are routinely performed, and if done early and frequently, they seem to more reliably cause the stricturing process to relent and achieve a durable result. The dilations have usually been started within 2–4 weeks of the final resection and done at 1–2-week intervals. With early treatment, only one to six dilations have been needed for a stable esophageal caliber. If begun later, after significant narrowing has occurred, the patients may again develop a fairly resistant stricture requiring many additional dilations or even resection.

Results of Stricture Resections

In our series of stricture resections at the University of Minnesota, up to four resections in the case of a 12.5 cm lye stricture were required to remove all involved tissue. Of the 19 stricture patients, 5 required 2 or more resections. For the other 14 patients, intraoperative traction accomplished bringing the ends together for a true primary repair (see Chap. 25: "A Flexible Approach to Long-Gap EA"). The growth response following an anastomosis under tension will essentially be completed within about 7 days, and reoperation will be easily done within about 10–12 days from the previous one. The next best time for the next resection would be 4–6 weeks later when the adhesions will be more filmy and less vascular. In this series, subsequent resections have been done from 1 week to 2 months after the previous resection, and the time interval resulted from a variety of factors. Some patients, for example, if they were handling secretions well, were discharged between resections which led to longer intervals.

A follow-up was completed at our institution for 12/19 patients from 0.7 to 7 years after completion of the stricture resections. All patients had fundoplications, usually before the stricture resection. The patients with the lye and congenital strictures, however, had the fundoplication after the stricture resections were completed. Endoscopy was completed in 12 patients and no residual strictures were seen. Mild reflux esophagitis on biopsy was found in 3/12, with the remaining having normal esophageal mucosa. Five patients remained on anti-reflux medications, although three out of five had no reflux symptoms. As is the case in EA repairs, after the stricture resections, usually no peristaltic motion existed below the anastomotic line and the esophagus emptied by sporadic uncoordinated contractions and the effects of gravity. Nevertheless, all patients were eating a normal diet, appropriate to their age. There were no reports of diet restrictions, dysphagia symptoms, or aspiration events.

Discussion and Conclusions

There is considerable variability in treatment of strictures across institutions, and few long-term data are available to provide guidelines. When the strictures are resistant to treatment, then resection and repair would appear to be the best option toward achieving this goal. This approach allows for the growth and utilization of esophageal tissue to make up the defect after resection which avoids the complications of various other replacement techniques. Importantly, once an essentially normal esophageal configuration has been achieved and reflux controlled, it is likely that these repairs will remain stable and should provide for the many long years of function that is necessary for the effective treatment of children. Because this is a relatively new approach, however, follow-up data are still needed.

This favorable outcome is in distinction to either the partial or complete gastric pull-ups or a colon interposition where the adverse consequences increase with time. With the stomach and GE junction, completely or partially in the chest, reflux becomes obligatory and little can be done about it. Either cervical or thoracic esophagitis will result even if the gastric mucosa becomes atrophic or large amounts of proton pump inhibitors are given. The reflux typically contains bile which has been shown to be the major cause of damaging effects [18]. A host of other problems will also be present ranging from anemia to reduced weight gain to aspiration and chronic pulmonary problems. For the colon, the organ dilates producing increasing difficulties from chronic aspiration, dysphagia, and difficulties in clearing food from the aperistaltic segment. The problems with these interpositions are discussed more fully in the chapters on their long-term results.

The resection of strictures described may require a technically more difficult operation than an interposition graft and even two or more resections to solve the problem. Although this may seem to be an elaborate overall approach,

the goal is for 70 good years without significant related problems, and our results suggest this is the most effective way to achieve it.

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The Esophagogastric Junction, Reflux, and Esophageal Atresia

42

Khalid M. Khan

Introduction

The lower esophageal sphincter (LES) is charged with maintaining a gating system that allows passage of ingesta into the stomach and, at the same time, acts as a barrier to reflux of gastric contents. Anatomically, the LES is a thickening of the circular muscle at the distal end of the esophagus, which itself is a tube that is under tension (Fig. 42.1). The LES interacts with the adjacent diaphragm to maintain integrity and pressure differences between the abdominal and chest cavities; this relationship also plays a role in relaxing the sphincter mechanism to allow normal passage of food boluses. The maintenance of the closed or tonic state of the LES is a property of its intrinsic structure and physiology. The major response of the LES is to relax when a swallow is performed, allowing aborally propagated food boluses to enter the stomach. While the typical terminology is that the sphincter "relaxes," muscular contraction is involved in opening the sphincter [1].

In patients with esophageal atresia (EA) with or without a tracheoesophageal fistula (TEF), primary structural defects may exist in the organization of the LES in addition to a shortened esophagus and the primary defect and fistula. The mechanism that facilitates opening of the LES as a response to a swallow may be intact prior to EA repair despite the esophageal defect. Long-gap EA is usually associated with extreme shortening of the lower esophagus; in such extreme cases, the LES may be the only appreciable lower remnant.

Surgery to achieve a primary repair of EA may have an impact on the mechanism by which the LES opens, by disrupting the vagus nerve. To perform a primary repair of long-gap EA, tension is necessarily applied to the lower esophagus; as a result, the LES may be lifted into the thoracic cavity, thereby compromising the role of the diaphragm in the maintenance of LES continence. Our own practice has been centered on the use of esophageal traction to achieve primary repair of long-gap EA and referrals from outside institutions arrive at various stages or EA repair or failed repair [2]. A large proportion of our patients have pure EA without a distal or proximal fistula where the lower esophageal pouch may be severely diminished (Fig. 42.2). We have used traction as a method to grow the esophagus and therefore be able to perform a primary repair with the goal of always using the patient's own esophagus [3]. Application of tension via traction to the lower esophageal pouch over several days clearly has an effect on the location of the LES with loss of the normal angle of His as the stomach is pulled upward.

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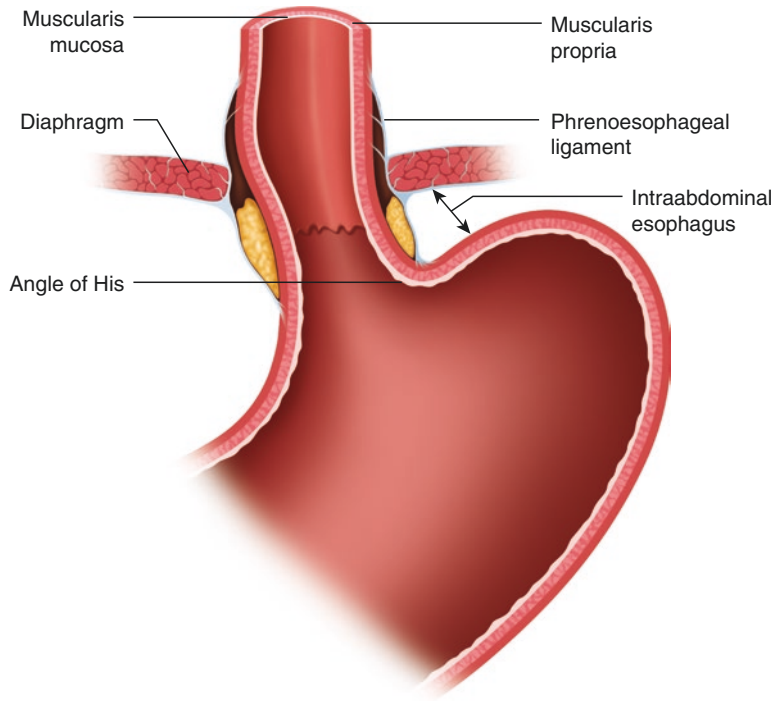

Fig. 42.1 The normal lower esophageal sphincter. (*A*) Muscularis mucosa, (*B*) muscularis propria, (*C*) phrenoesophageal ligament, (*D*) diaphragm, (*E*) intra-abdominal esophagus, (*F*) angle of His

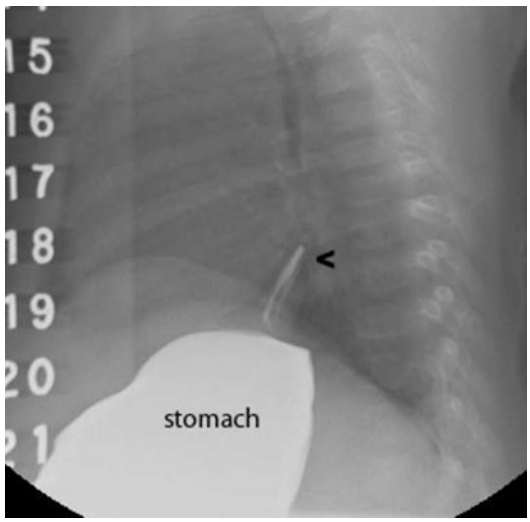

Fig. 42.2 Small lower esophageal pouch in a case of long-gap esophageal atresia. Note the normal-appearing stomach and normal esophagogastric junction

Gastroesophageal reflux (GER), a recognized problem in patients with EA, is more likely after long-gap EA repair [3, 4]. Relocation of the stomach into the abdomen and/or a Nissen fundoplication may be necessary to reestablish anatomic integrity (as well as treat the GER).

In the first half of the chapter, normal LES structure and function and the mechanisms for common abnormalities of the LES are reviewed, while in the second half of the chapter, these mechanisms are used to explain the LES structure, function, and mechanism of GER in patients with EA.

Structural Anatomy

Morphologically, the gastrointestinal tract changes from a tubular to saccular form at the transitional zone between the esophagus and

stomach called the esophagogastric junction (EGJ). At this point, the mucosal epithelium changes from stratified squamous to simple columnar. In the chest, the esophagus is subjected to negative pressure generated by respiration, whereas in the abdominal cavity, the stomach is exposed to positive pressure.

Anatomically, at the tenth thoracic vertebral level, the esophageal body enters the hiatus in the right crus of the diaphragm and ends in the LES, which is immediately above the EGJ. The phrenoesophageal ligament (which originates from the transversalis fascia of the diaphragm) inserts on the lower esophagus and aids in the fixation of the LES; the LES lies above and up to 2 cm below the diaphragm (Fig. 42.1).

Structurally, the lower esophagus has smooth muscle in two muscular layers: the thicker muscularis propria and the inner muscularis mucosae. The outer layer (propria) is much thicker; it is described as having a longitudinal outer and circular inner layer (Fig. 42.1). The esophagus is kept in tension between the EGJ and the upper esophageal sphincter: transection of the normal esophagus will result in retraction of both ends. The primary neural supply of the LES is via the vagus nerve. Between the longitudinal and circular smooth muscle layers of the muscularis propria lies the Auerbach's (myenteric) plexus; farther in, the Meissner's plexus lies in the submucosa and is primarily sensory. In the esophagus, the intramural density of ganglion cells increases aborally and is maximal just above the LES [1]. Please also see Chap. 35 for histological variations of the neuronal and muscular components of the esophagus in patients with EA.

The function of the esophageal muscle differs in the esophagus (versus in the LES), but the anatomic movement in the muscle fibers is the same. To achieve muscle contraction by shortening of the muscle, the fibers are arranged obliquely and cross each other. The angle at which muscle fibers cross determines their function; in the body of the esophagus, fibers cross at an angle of more than 45° and the resulting motion is propagation of food boluses downward [1]. At the LES, fibers cross at an angle of less than 45° and contraction pulls the LES open [5].

Like the muscle of the body of the esophagus, the LES maintains spontaneous muscle activity, allowing it to remain contracted without fatigue [1]. The force generated to keep the LES closed is not as strong as the force of a true occluding sphincter; nonetheless, the LES is able to keep acid out of the esophagus, most of the time, in the physiologically normal state.

A number of structures come together at the esophageal hiatus to create the complex occlusive function of the LES system [6]. It consists of the muscular elements of the diaphragm, ligaments, and the LES itself (Fig. 42.1).

The second part of the sphincter mechanism of the lower esophagus is the diaphragm. The crural diaphragm develops from the dorsal mesentry of the esophagus and is innervated from the costal diaphragm. Humans are able to swallow only if the crural muscles relax sufficiently during the passage of food boluses [7]. It can be shown that electromyographic activity in the diaphragmatic crural muscles stops during the swallowing process and that, simultaneously, the esophageal hiatus widens, allowing food to pass. The converse, i.e., tightening of the crura does not appear to contribute to the normal LES closed state [1]. However, tightening of the crura does contribute to LES pressure during inspiration and with increased abdominal pressure from maneuvers such as coughing; such additional pressure may be as much as 150 mmHg [8]. This section of the diaphragm encircles the LES, which can freely slide within the hiatus.

A third mechanism that helps prevent regurgitation is the natural angle of the esophagus as it becomes the stomach. The angle of His creates a valve-like effect that protects against GER (Fig. 42.1).

Physiology

In adults, the LES is characterized manometrically as a high pressure zone of 3–5 cm long that marks the lowest extreme of the esophagus. The proximal LES border is up to 2 cm above the squamocolumnar junction; more than half of the LES lies in the abdominal cavity. The LES is tonically closed with a resting pressure of

10–30 mmHg, although a pressure as low as 5 mmHg is enough to maintain function [6]. The area is differentiated from the esophagus above it by muscular, neuronal, and biochemical characteristics. Per radiologic assessment, it is an area of thickened muscle; it cannot be easily palpated in an operative field as a characteristic area, but it can be dissected in an autopsy specimen. Yet when examined on a computed tomography-position emission tomography (CT-PET) scan, the LES displays a very high signal [1]. The density of circular fibers of muscle increases progressing caudally from about 3 cm above the EGJ. The result is progressive thickness until the terminal portion of the esophagus, with an increase in the number of asymmetric inner muscles of the circular muscle layer of the muscularis propria [9]. The muscles on the side of the lesser curvature of the stomach retain their configuration and form the short muscle "clasps," whereas the muscles on the side of the greater curvature become the "oblique gastric sling" fibers [10]. This muscular asymmetry results in similar asymmetry of the intraluminal pressure zone. This pressure zone is affected by myectomy and by displacement the LES upward into the thoracic cavity. But, in experimental models, dissection of the phrenoesophageal membrane had no effect on LES pressure (Fig. 42.1). Clasps have significant tone at rest and a poor response to cholinergic stimuli; in contrast, sling fibers have little resting myogenic tone, but respond well to cholinergic stimuli (also see next section for a description of neural innervation) [11]. Resting tone therefore is primarily maintained by the unique properties of clasps—a combination of the properties of the muscle itself and neural excitation. The circular muscle maintains most of its elevated myogenic tone by entry of extracellular calcium through the L-type channels [12]. These channels are most abundant in clasps; less expression of such channels is seen in sling fibers.

The circular fibers of clasps are highly innervated by inhibitory motor neurons that release nitric oxide (NO); sling fibers have few such neurons [13]. NO is the major inhibitory neurotransmitter that mediates neurogenic smooth muscle relaxation in the gastrointestinal tract; it accounts for 34 % of all neurons in the myenteric plexus and is the most abundant neurotransmitter found in the LES [14]. The gastric sling, especially the left lateral part on the posterior side, is innervated mainly by cholinergic fibers; it has an alternative calcium-handling source, whether for resting tone maintenance or contraction [15]. In the resting state, this area demonstrates the highest manometric pressure [16]. Therefore, part of the resting tone is due to acetylcholine (ACH) release from excitatory neurons [17]. The balance between inhibitory and excitatory neural influence and myenteric NO appears to regulate LES tone.

All swallows are followed 1 to -2 s later by a drop in LES pressure, which lasts for several seconds; however, not all swallows create propagating motor activity in the esophageal body (Fig. 42.3). The process in the LES is a combination of cessation of tonic contraction and inhibition of the muscle by inhibitory neurons that are both nonadrenergic and noncholinergic (NANC). As noted above, there is vagal and peripheral control of the LES [17]. Peripheral control is related to postganglionic cells that mediate LES relaxation via the release of NO and, to an extent, vasoactive intestinal polypeptide (VIP) [18]. With vagal control, the fibers that supply the LES likely enter the musculature above the lower third of the esophagus; highly selective vagotomy in this area does not affect LES resting pressure or LES relaxation, and the effect of cholinergic stimulation is retained.

LES pressure exhibits diurnal variation. It is highest at night and lowest after meals— timed with motor activity of the stomach in reacting to food (especially fat), circulating peptides, and hormones. In healthy volunteers, the administration of cholecystokinin (CCK) results in LES relaxation [19]. Hormones have different effects depending on their site of action (such as pre- or postganglionic) and can act in more than one place. For instance, in cats, CCK stimulates inhibitory nerves that mediate physiologic LES relaxation (an indirect effect); it also has a direct excitatory effect by stimulating excitatory receptors in LES musculature, the overall effect being LES relaxation [20].

Manometry and Impedance

Contrast radiography has always been the first-line diagnostic test for disorders of the esophagus and LES. It is very sensitive for morphologic abnormalities as well as for normal anatomy. Manometry has been the most discriminative test of esophageal and LES function; more recently, impedance has been combined with manometry to simultaneously evaluate the relationship between bolus transit and esophageal pressure. Electrical impedance of the surface epithelium of the esophagus is reduced with passage of food boluses [1]. As the bolus is transported downward in the esophagus, its arrival at any point is preceded by an increase in luminal pressure, indicating an increase in esophageal wall tension [21]. As the bolus is transported distally, toward the stomach, the decrease in impedance becomes is prolonged.

The increase in pressure opens the esophageal lumen and produces a peristaltic wave as the wall tension rises, correlated with an axial lengthening of the esophagus (Fig. 42.3) [22]. This mechanism explains why a correlation between bolus transit time and pressure amplitude cannot be established in impedance and manometry recordings [22]. In the distal esophagus, impedance remains low for an extended time, during which the LES system is opened to allow the bolus into the stomach (Fig. 42.3). A relatively new technique to visualize esophageal pressure is high-resolution manometry (HRM) [23, 24]. HRM uses a large number of closely placed side holes or solid-state pressure transducers. It allows a more detailed view of pressure in the LES.

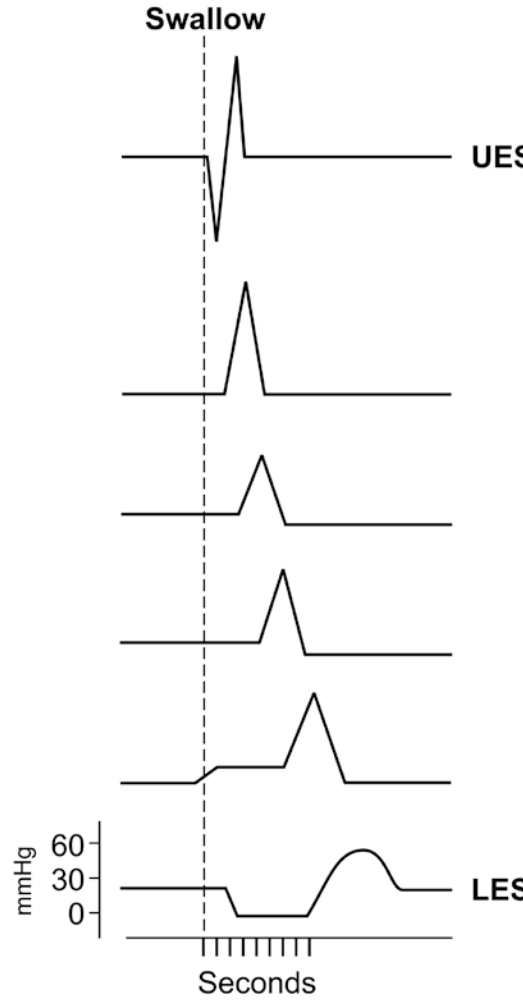

Fig. 42.3 Normal propagating manometric pressure wave through the esophagus. *UES* upper esophageal sphincter, *LES* lower esophageal sphincter

Transient Lower Esophageal Sphincter Relaxation

Other than gating the entry of food into the stomach, the LES system is most significant for producing GER, especially GER disease (GERD). Transient LES relaxation (TLESR), the hallmark of GER, is characterized as a sphincter relaxation that is not induced by swallowing. But TLESR is actually a physiologic process that occurs about three to six times per hour [25]. It is considered the normal mechanism that enables venting of gas from the stomach (i.e., belching) [26]. The subcardiac gastric region has the lowest threshold for triggering TLESR, so is likely the region primarily responsible [27]. Distention of the stomach caused by intragastric air and food triggers TLESR [17–20, 28]. Foremost, TLESR involves relaxation of the LES by activation of inhibitory neurons in the myenteric plexus by the vagus [29]. Suppression of crural motor activity results in relaxation of the crural diaphragm [29]. Similarly, lower esophageal peristalsis is suppressed. Contraction of the

distal esophageal longitudinal muscle leads to esophageal shortening [29]. During TLESR, longitudinal muscle contraction occurs in the distal esophagus, progressing retrograde; such contraction may be more forceful than the normal longitudinal muscle contraction associated with a swallow [30]. The sensory part of this reflex involves a signal from the stomach projected to the brain through afferent sensory fibers of the vagus [31]. The relaxation of the crural diaphragm that occurs simultaneously with LES relaxation is also mediated through vagal afferents [32]. The motor signals to the LES and crural diaphragm are conducted through the efferent motor tract of the vagus [33]. These signals are relayed to the myenteric plexus, from which they are distributed throughout the esophageal body and LES [33]. A number of peripheral factors have also been shown to trigger TLESR [34]. Overall, this reflex acts as a protective mechanism by preventing accumulation of excess amounts of gas in the stomach [6].

TLESR accounts for more than two-thirds of acid reflux episodes and is the main mechanism leading to acid reflux [6]. Yet most studies show a similar rate of TLESR in healthy individuals and in patients with GERD [35]. Thus, a greater proportion of TLESR is associated with GER in GERD patients [36]. An additional factor that facilitates reflux during TLESR in GERD patients (as compared with healthy controls) is a slightly higher trans-sphincteric pressure gradient before and during TLESR, caused mainly by an increase in intragastric pressure [37]. Furthermore, the pressure gradient is greater during TLESR accompanied by acid reflux [37]. Increased compliance of the LES in GERD patients has also been documented [38]. Increased compliance of the GEJ was found in GERD patients with hiatal hernia as well as in patients without hiatal hernia [38]. In symptomatic GERD patients without hiatal hernia and normal subjects, it was noted that GERD patients show a more distensible GEJ compared with controls [39]. Both primary peristalsis and more commonly secondary contractions are the motor event terminating GER episodes [40].

Pathologic GER is known to occur in particular patterns. One study found that, postprandially, the rate of GER episodes increased up to seven times [41]. That increase was related to a fivefold increase in the rate of TLESR and to an increase in the proportion of TLESR accompanied by GER [41]. The mechanism responsible for the postprandial increase in TLESR likely involves an increase in proximal gastric volume, activating tension receptors in the proximal stomach, yet the percentage of TLESR associated with acid reflux does not relate to proximal gastric volume [37].

Another pattern of significance for GER is nocturnal reflux, nocturnal GER events often occur when the patient is awake or arouses from sleep and not necessarily, while LES pressure is low during sleep [42]. Other mechanisms (such as straining and coughing) are responsible for the remaining GER episodes and are important in patients with severe disease associated with a hiatal hernia.

Despite the frequency of TLESR, additional mechanisms can protect against GER. In the fasting state, LES relaxation induced by pharyngeal stimulation is not associated with inhibition of the crural diaphragm or with acid reflux [6]. Postprandially, few of the pharyngeal stimuli result in crural diaphragm inhibition; GER was found only when LES relaxation was associated with crural inhibition [6]. Thus, simultaneous diaphragm inhibition and LES relaxation are necessary in order to generate GER.

Hiatal Hernia

In patients with a hiatal hernia, the LES cannot anatomically be kept closed in a coordinated fashion. The EGJ is transposed into the chest, thereby shortening the esophagus. The LES is rendered incompetent as a result of loss of tension in the esophagus; such tension is necessary to maintain LES form [1]. By the same mechanism, esophageal motility is reduced in GERD patients. The LES may not open properly in about 4% of GERD patients [43]. The relationship between TLESR in patients with a hiatal hernia is not clear [44]. TLRSR is less important for reflux in GERD patients with (versus without)

a hiatal hernia; only 40 % of acid reflux episodes are associated with GER [44]. Reflux in patients with a hiatal hernia is more often related to low LES pressure or to straining during periods with low LES pressure and otherwise normal LES relaxation [44]. As noted above, compliance of the EGJ in GERD patients with a hiatal hernia is increased.

Surgery for Gastroesophageal Reflux

A fundoplication is the standard surgical intervention for GERD patients and is effective in reducing GER (whether involving acid reflux or not) [45]. The mechanisms for its effectiveness are not clearly understood. When a hiatal hernia is repaired, the EGJ and part of the LES system are reconstituted. Transposition of the herniated stomach back into the abdomen reestablishes the stretch of the esophagus and therefore the occlusive state of the LES [1]. By definition, a fundoplication wrap decreases the distensibility of the EGJ but also that of the upper gastric cavity [46].

The effect on the gastric cavity appears to be more complex. One study showed that proximal gastric compliance was not significantly different in patients who underwent a fundoplication, in GERD patients, and in healthy controls [47]. Furthermore, although vagal damage is a concern with surgery, a fundoplication was shown to increase gastric emptying, with vagal damage in only 10 % of patients [48]. Moreover, a fundoplication decreases the rate of TLESR [49]. And the proportion of TLESR associated with reflux also decreases after a fundoplication [49].

The Closed Lower Esophageal Sphincter Achalasia

Achalasia, which means “inability to relax,” is the best known disorder that affects the LES as a primary problem. In reality, the term is a misnomer at some levels because the LES is unable to contract its muscle wall and thus unable to open [1].

Idiopathic achalasia involves Auerbach’s plexus and is characterized by an absence of ganglion cells in the involved portion of the esophagus [50]. Ganglion cell degeneration is prominent in the early years of achalasia, with progressive loss of neurons [51]. Absent or incomplete relaxation of the LES is secondary to defects in the postganglionic neurons; such neurons may be reduced in number, absent altogether, or normal but functionally abnormal, or they may terminate without more proximal connections [52]. In some patients, the intramural ganglion cells are diminished to a lesser extent in the LES [53]. In others, they are missing in the body of the esophagus as well as in the LES. Although propulsive waves are no longer detectable in patients with achalasia, spontaneous activity may cause pronounced hypertrophy of the muscle wall of the esophageal body, where there are many ganglion cells. The LES is the only segment of the esophagus that does not undergo hypertrophy, likely because it has only a few ganglion cells.

Achalasia can have a number of different causes [1], which may be the reason for the heterogeneous impedance manometry measurements in such patients [54]. The classic findings are increased LES pressure with incomplete relaxation or opening of the LES and loss of distally propagating contractions. The disorder is progressive. In a study of children whose achalasia was diagnosed by barium swallow and by absence of peristalsis per manometry, 57 % of them had normal LES pressure, 13.8 % had no LES relaxation, and 87 % had some LES relaxation [55]. In a study of adult patients without peristalsis, 81 % of them had incomplete LES relaxation and 19 % had intermittent normal LES relaxation [56].

Clinically, dysphagia and respiratory problems are typical. The esophagus eventually distends distally, because of the presence of food over the long term. Interventional treatment with sphincteric botulinum toxin injection, pneumatic balloon dilation, and myectomy can be effective. If medical management is preferred, the use of nitrates and calcium channel blockers can also be effective.

The Lower Esophageal Sphincter in Esophageal Atresia

Limited data have been published on LES anatomy or function in EA patients. A preoperative study of EA patients, with or without a TEF, found abnormalities of the myenteric plexus [57]. Similarly, in an animal model of EA, multiple anomalies in the vagus and its innervation were reported [58]. However, we previously demonstrated that at least the gross morphology of the LES is well preserved even when the lower esophagus is extremely short (Fig. 42.2). A manometric study of 20 neonates before EA repair showed that the LES was 8–14 mm long: in 84 % of the patients, LES pressure ranged from 22 to 35 mmHg; in 16.7 %, LES pressure was low; and in 8.4 %, LES relaxation was incomplete [59]. Another preoperative manometric case study of long-gap EA showed peristaltic contractions in the proximal esophagus that appeared to be propagated into the distal esophageal pouch, culminating in normal LES relaxation [60, 61].

Atresia Repair and the Lower Esophageal Sphincter

Some authors have argued that damage to the vagus and/or its branches during surgical repair may cause the motor defects in EA patients, including the discoordination of the LES (see next several section for details) [60–62]. One of the most compelling findings in support of that argument came from the preoperative data from Shono et al. mentioned above [60, 61]. EA repair was followed by abnormal motility and LES relaxation, suggesting that the abnormal motility seen after the typical EA repair may be the result of denervation from intraoperative mobilization. In contrast, an experimental canine study found that cervical vagotomy had no significant effects on the LES, despite a low resting LES pressure, thoracic disruption of the vagus or esophagus, resection of the esophageal branches of the vagus, and phrenic nerve resection [63].

In an esophageal transection model in rats, Montedonico et al. [64] looked at the difference between primary EATEF repair and long-gap EA. Using pull-through perfusion manometry, they measured LES pressure, crural sling pressure (CSP), and the length of the intra-abdominal segment of the esophagus (LIAE) (Fig. 42.1) in 20 rats before and after resection of 15 mm of the cervical esophagus (and in eight controls before and after esophageal transaction). In the 20 rats, mean LES pressure decreased from 44.9 ± 17.4 to 30.9 ± 12.3 mmHg and mean LIAE from 17.9 ± 2.8 to 15.8 ± 2.4 mm. But in the eight controls, LES pressure and LIAE did not significantly change. CSP did not change significantly. Montidonico et al. concluded that postoperative reflux in EA patients might be, in part, caused by damage to the vagus and/or its branches.

Dutta et al. reported similar findings in a case-control study of 27 children (mean age, 30 months) after EATEF repair [65]. Postoperatively, mean LES pressure was lower in the study patients (12.2 ± 6.8 mmHg) than in the controls (16.8 ± 4.3 mmHg). Mean LES pressure was 12.0 ± 7.1 mmHg in the study patients with no GER; 12.3 ± 3.7 mmHg, mild GER; 11.0 ± 5.7 mmHg, moderate GER; and 6.9 ± 5.6 mmHg, severe GER.

According to these studies, postoperative LES pressure at rest does tend to be low in EA patients, possibly related to disruption of LES physiology during repair. Yet low LES pressure does not appear to account for the symptoms described in children. The lack of a relationship between LES pressure and GER was also supported by a study of 20 children (mean age, around 111 months) whose GER was improved by a fundoplication; despite signs and symptoms of GER and esophageal manometric abnormalities, their postoperative LES pressure was normal [66].

Manometrically the LES of the EA patient behaves somewhat similar to achalasia. Swallows may be propagated in the proximal portion of the esophagus in the normal manner in some individuals and we have found the manometric force generated to be pronounced. There is no propulsive pressure change in the distal esophagus only simultaneous contractions that are variable in amplitude but generally of low amplitude. There is no relaxation of the LES to swallows and as

mentioned above the resting LES pressure may be reduced.

Hiatal Hernia After Esophageal Atresia Repair

The potential for a hiatal hernia as an iatrogenic phenomenon of EA surgery is understandable especially in long-gap patients, in whom tension is necessary to achieve primary repair. In our patients that undergo traction of the lower esophageal pouch for several days the EGJ can be transported cranially and the normal configuration and relationship with the angle of His is lost until a fundoplication is performed (Figs. 42.2 and 42.4). A study using esophageal manometry to evaluate LES function and motility of the esophagocardiac region found that patients who underwent operations for pure atresia and non-EA patients with hiatal hernias considered to have GER showed reduced LES pressure and LES length and esophagocardiac motor abnormalities [67]. LES pressure, length, and motility of the esophagocardiac region improved in patients who underwent an antireflux operation.

Hiatal hernia as a late complication is also likely related to growth of the individual [68]. It is a common finding in adults who, as children, underwent EATEF repair. One study of adults (mean age, 36 years; range, 21–57 years) found symptomatic GER in 34 %, and endoscopic findings included a hiatal hernia in 28 % [4].

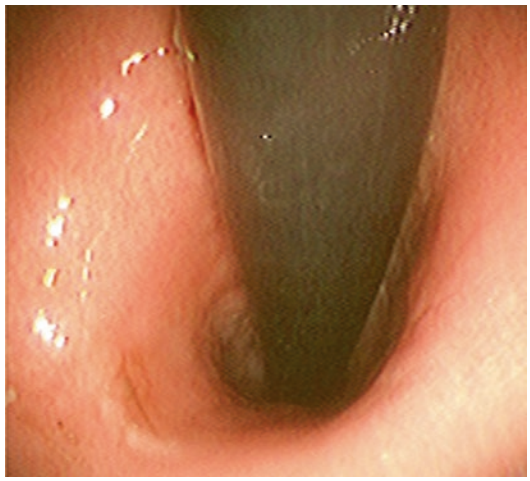

Fig. 42.4 Endoscopic view of the esophagogastric junction (EGJ) after EA repair having undergone traction in an infant. The EGJ is pulled upward and has lost the normal configuration. The patient subsequently underwent a Nissen fundoplication

Gastroesophageal Reflux After Esophageal Atresia Repair

GER is universally reported as a problem after EATEF repair [68–73]. An Australian long-term follow-up study showed that older symptomatic patients had a high risk of complications: 63 % had reflux symptoms and 19 % had severe symptoms [68]. Another long-term study of 227 EA patients, spanning more than two decades, found GER in 127 patients (58 %); 56 patients (44 %) required an antireflux procedure [74]. In a series of 31 EATEF patients for whom medical treatment was unsuccessful, 14 patients (45 %) underwent a Nissen fundoplication [75]. A study of adults found that GER was a common problem that impaired quality of life in 30 % of patients [69]. Tovar et al. found major symptoms and acid clearance problems related to ineffective peristalsis in the distal esophagus in relation to GER [70].

Long-term follow-up of children after EA repair has revealed disordered esophageal motility in almost all of them [68–74, 76]. Apart from low LES pressure and lack of propagating motility, esophageal contractions are simultaneous and weak, especially in the lower esophagus [62, 65, 76]. Low LES pressure in such patients has been associated with more severe reflux and aspiration pneumonia [65]. However, no correlation has been found between pulmonary problems and the presence of GER, esophagitis, or esophageal dysfunction [74, 77].

Fundoplication After Esophageal Atresia Repair

There are few data on medical treatment of GER in EA patients and none specifically aimed at identifying specific pharmacological regimens. It would be reasonable that the patients are treated in a simi-

lar manner to the general population of reflux patients. In most series of EA patients, significant proportions undergo fundoplication and this may be up to 50% [75]. In the case of long-gap EA, a fundoplication is often necessary early after EA repair, to restore the EGJ in the abdominal cavity. It has been argued that, when the EGJ is displaced, simply restoring it in the abdominal cavity without a fundoplication should be adequate to treat GER [1]. The reasoning is that the shortened esophagus that has lost its natural tension is once again placed under tension and the configuration of muscle fibers is reestablished and therefore the function of the sphincter is restored [1, 78]. This method (simply restoring the EGJ in the abdominal cavity) has been used extensively with good success even when compared with a fundoplication though not in the EA population [78].

To an extent, simply restoring the EGJ in the abdominal cavity may have some advantages for EA patients. In the study by Curci et al. discussed earlier, of the 14 patients (out of 31) who underwent a Nissen fundoplication, five had prolonged dysphagia requiring supplemental gastrostomy feeding [75]. Of those five patients, four underwent postoperative manometry and extended pH monitoring, which revealed normal LES pressure (greater than 15 mmHg), normal pH results, and marked esophageal dysmotility. Curci et al. postulated that the fundoplication created a mechanical obstruction for those patients with a dyskinetic esophagus that cannot generate the pressure to open the LES. To avoid such a complication, they advised deferring antireflux surgery, if possible, in those patients with GER and marked esophageal motility abnormalities. Marked esophageal motility abnormalities are also a universal feature of EA repair, so no operation is ideal. In our long-gap EA patients, almost all of whom had a fundoplication, we noted that normal feeding patterns did subsequently develop [79].

Mechanism of Esophageal Reflux in Patients with Esophageal Atresia

Symptoms of GERD and esophagitis are common in patients with a history of EA [68]. The typical mechanism of pathologic GER however may not apply to EA patients. Studies are lacking that demonstrate TLESR, whether physiologic or pathologic, EA patients. Our present understanding of TLESR and LES abnormalities in EA patients suggests that TLESR does not occur because of the lack of an intact vagal feedback for generating TLSER. Nevertheless, both GER (as demonstrated by pH studies) and esophagitis are prevalent in EA patients and appear to be major issues when they become adults. If the original defect was long-gap EA, the problems and symptoms appear to be worse. A number of factors clearly play a role. First, a hiatal hernia not only from tension during EA repair but also the result of constant upward movement of the LES with growth and development, perhaps related to unequal growth of the esophagus versus the rest of the body. Secondly the compliance of the LES is likely reduced and as noted above the LES pressure may be low. Finally refluxed gastric contents cannot be cleared from the lower esophagus by the normal secondary peristalsis. As noted these pathological features apart from the last one are affected by fundoplication and this may account for the positive response seen in EA patients to fundoplication. Caution needs to be exercised given that the LES is somewhat like achalasia and a tight fundoplication may make esophageal clearance worse.

Summary

The LES is morphologically normal in patients born with EA, despite the type of lesion or the length of the gap. The LES has the potential to function; however, after EA repair, the LES does not open normally and may be displaced into the chest and cannot naturally relax. GER in such patients is related to this hiatal hernia and to the poor clearance of the lower esophagus of acid refluxate. TLESR, as a mechanism for GER, is less clear in the absence of normal vagal feedback and it is yet unclear as to whether it occurs in patients with a history of EA repair. The fundoplication wrap does improve GER but can be to worsen the obstruction that naturally exists in the LES of such patients, but it remains the only method for treating GER.

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43 Management of Gastroesophageal Reflux After Esophageal Atresia Repair

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Introduction

Gastroesophageal reflux (GER) in infants, also known as chalasia of infancy, represents a common physiological phenomenon during the first year of life [1–3]. Regurgitation occurs more than once a day in 60–70 % of 3–4-month-old infants and decreases to approximately 20 % in infants between 6 and 7 months of age. By 10–12 months of age, less than 10 % of infants experience regurgitation [4–6].

Gastroesophageal reflux disease (GERD) is one of the most common gastroenterological disorders in infants and children and continues to pose complex diagnostic and management problems. GERD is defined as involuntary passage of gastric contents into the esophagus that leads to symptoms or tissue damage.

GER can be categorized as either physiologic or pathologic. Physiologic, or functional, GER is a regurgitation that leads to no sequelae, and thus patients do not suffer complications related to the reflux. These patients have no underlying predisposing factors or conditions for GER and experi ence no growth or developmental delays. They are often referred to as "happy spitters" and usually don't require pharmacologic treatment [1, 4, 7]. In contrast, children with pathologic GER usually experience complications from the reflux. These patients may develop malnutrition, failure to thrive, esophagitis, or respiratory disorders, as well as complications including esophageal strictures and Barrett's esophagus [1–3, 8–11].

GER in the pediatric population is characterized as immaturity of the lower esophageal sphincter (LES) [9]. The LES functions as a barrier between the esophagus and the stomach by preventing reflux [7]. It has been shown that in infancy and childhood, the LES transiently relaxes leading to reflux of gastric contents [3, 12]. During swallowing, food is propagated down the esophagus via esophageal peristalsis. The most distal portion of the esophagus lies in the abdomen, and food enters the stomach upon relaxation of the LES. This portion of the esophagus, known as the abdominal esophagus, is pivotal in preventing reflux. It is often referred to as the high-pressure zone because it denotes the location of the LES. Initially described in 1956, this high-pressure zone is composed of and influenced by many factors such as an adequate intra-abdominal esophageal length, the presence of the phrenoesophageal ligament, a

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normal functioning diaphragm, and an appropriate gastric emptying. Anatomic or other abnormalities of these components can predispose to GERD. In adults, studies have shown that individuals with 1 cm or less of intra-abdominal esophagus are more prone to reflux when compared to those with an intra-abdominal segment longer than 3 cm [13]. An increase in intra-abdominal pressure due to poor gastric emptying has been found to increase the number of reflux episodes and contribute to incompetence of the LES [14]. Additionally, it has been shown that reflux symptoms usually occur when sphincter pressures drop to less than 5 mmHg [7, 15, 16]. Unrelated to the above noted factors, the supine position may also predispose to reflux [10].

Reflux Strictures

Fortunately, GERD in infancy and childhood usually becomes less evident with age [9, 17]. Unfortunately, the long-term complications of GERD in infants and children can result in esophageal strictures and, in more complicated cases, Barrett's esophagus [6, 9, 11]. In a strict sense, an esophageal stricture is defined as a long-standing narrowing of the esophagus, usually due to scarring, and is commonly caused by acid irritation [6, 18]. In the context of children with esophageal atresia, an anastomotic stricture is generally present at the time of repair and may progress due to GERD.

Risk factors associated with severe GERD, and possible stricture formation during infancy and childhood, include neurological impairment, esophageal atresia/tracheoesophageal fistula (EA/TEF), and chronic lung disease [1]. The most common acquired causes of esophageal stricture are ingestion of corrosives, GERD, and after repair of esophageal atresia. Symptoms are generally gradual in presentation, with initial difficulty in tolerating solids, and followed by intolerance to liquids [9].

The incidence of an esophageal stricture secondary to untreated GERD varies from 15 to 30 % [9]. In infants and children, the mean age at presentation is 5.5 years. Studies used to diagnose reflux esophagitis in infants and children include barium esophagram at the time of an upper gastrointestinal radiographic series and esophagoscopy with biopsy. For peptic strictures greater than 10 mm, the barium esophagram is more sensitive. The barium esophagram is also superior in diagnosing achalasia and diffuse esophageal spasm, although esophageal manometry is necessary for definitive diagnosis. The gold standard for identifying mucosal disease caused by GERD is endoscopy and biopsy [10, 18]. This allows for a complete evaluation of the esophagus and, more importantly, exclusion of malignancy [6, 7, 9]. 24-h pH probe monitoring and impedance studies have also been useful in confirming GERD secondary to acid reflux and to distinguish GERD from eosinophilic esophagitis [6, 7, 10, 12].

Management of esophageal strictures varies widely among institutions. A number of management strategies are possible and include bougienage and medical therapy, fundoplication without dilatation, preoperative esophageal dilatation followed by fundoplication with intraoperative and postoperative dilatations, and resection with interposition grafting or primary anastomosis [8, 16]. In contrast to adults where the usual esophageal dilatation is endoscopic dilatation, in the pediatric population, the usual approach is balloon dilatation, bougie dilation, or operation [8]. Dilations are usually ineffective if reflux is not treated. Factors that impact the success rate of dilation include age of presentation, location of the stricture, degree of tightness, length of stricture, number of strictures, and previous failures. Operative repair is recommended in patients who fail nonoperative management [8, 9, 11].

Complications Following EA Repair

EA was first described in the seventeenth century as a congenital interruption of the esophagus. It took almost 250 years before Haight successfully

repaired a baby in 1941 with EA/TEF in a single-stage operation [19].

The incidence of EA is reported as 1 in 2,500–3,000 births [20]. The survival of children with EA/TEF has improved significantly over the past 40 years and currently is greater than 95 % [20, 21].

The most common postoperative complication of EA repair is an anastomotic stricture, which occurs in 18–50 % of patients [11, 22, 23]. Factors leading to development of a stricture include the gap length, anastomotic tension, anastomotic leak, GERD, and possibly a two-layer anastomosis. The most common presentation is intolerance to feeding. When an infant or child develops new symptoms of feeding intolerance after EA repair, an esophagram should be obtained to evaluate the esophageal anastomosis. When present, an anastomotic stricture appears as an abrupt change in esophageal caliber at the anastomosis (Fig. 43.1).

The initial management of esophageal strictures after EA/TEF repair is esophageal dilation. We prefer to utilize balloon dilation as it allows for gradual and progressive dilation under fluoroscopy. Additionally, by using contrast to fill the balloon, the length of the esophageal stricture can be determined [22, 23]. Fortunately, most esophageal strictures can be managed with dilation, although some require multiple dilations for resolution. Rarely, the anastomotic stricture is recalcitrant to dilations, usually because of its length or density. In these circumstances, resection with a primary anastomosis or esophageal replacement may be needed.

Recurrent TEF is seen in up to 10 % of patients and usually occurs weeks to months after the initial repair [24]. These patients are often premature with a lower than expected birth weight or an anastomosis complicated by leak [20, 24]. When a recurrent TEF develops, babies present with reflux, pneumonia, or symptoms of tracheomalacia. As with strictures, the diagnosis can often be confirmed on an esophagram which will show contrast entering the trachea through the fistula. Initial management is conservative with cessation of oral feeds and administration of antibiotics if pneumonia has developed [24]. After stabilization, the recurrent TEF can be addressed.

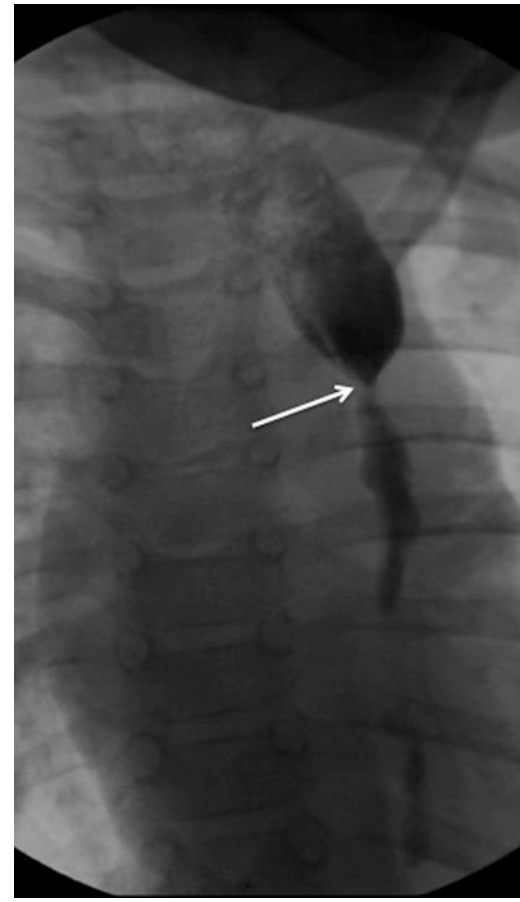

Fig. 43.1 This esophagram in an infant after esophageal atresia repair shows an anastomotic stricture (*arrow*)

Anastomotic leaks are not uncommon and can occur in up to 15 % of patients. The leak is usually identified several days after operation [22]. Babies most frequently present with an increase in chest tube drainage. However, they can present with pain, distress, and sepsis. Treatment is usually supportive as most leaks will close without operative intervention with adequate drainage.

Other complications following EA repair include GERD, dysphagia, pulmonary infections, asthma, and tracheomalacia [20, 21, 25, 26]. Later complications encountered are Barrett's esophagus, tracheomalacia, esophageal dysmotility, feeding problems, scoliosis, and, rarely, esophageal carcinoma [20, 25].

Anti-reflux Procedures and Lower Esophageal Motility

Prior to the 1990s, the majority of patients with GERD were treated with an operation due to lack of good medical therapy. Recently, fewer anti-reflux procedures are being performed due to improved pharmacotherapeutics and lifestyle modifications (i.e., dietary changes and sleep position) [4, 6, 9, 10]. Presently, anti-reflux procedures should be considered in patients who have failed medical management, patients on prolonged medical management, patients with complications due to GERD (i.e., esophageal strictures, esophagitis, Barrett's esophagitis, and pulmonary infections), or patients with symptoms and neurologic disorders [6].

Currently, the laparoscopic Nissen fundoplication is the most common procedure performed in both adult and pediatric populations for treatment of GERD [4, 15, 17]. Since the early reports of laparoscopic fundoplication in the early 1990s, significant advancements have occurred in the surgical approach in infants and children. Currently, laparoscopic Nissen fundoplication improves symptomatic disease in over 95 % of children and carries a morbidity rate of less than 5 % and a mortality rate less than 1 % [15, 17].

Regardless of the type of anti-reflux procedure performed, it is important to create an adequate length of intra-abdominal esophagus, accentuate the angle of His, increase the pressure barrier at the esophagogastric junction, and approximate the crura. These maneuvers should increase the resistance of retrograde flow across the lower esophageal sphincter due to an elevated residual lower esophageal sphincter pressure [7, 12, 17]. Techniques other than Nissen's have also been described and include the Thal procedure (anterior 180° fundoplication), Toupet operation (posterior 270° fundoplication), Watson fundoplication (anterior 120 fundoplication), and the Boix-Ochoa technique (restoration of intra-abdominal esophagus and recreation of the angle of His).

In a recent multi-institutional prospective, randomized trial, the effect of disruption of the phrenoesophageal membrane during laparoscopic Nissen fundoplication in relation to subsequent wrap herniation and the development of a hiatal hernia was evaluated [27]. It was shown that patients who did not have the phrenoesophageal membrane divided had a significantly lower likelihood of developing postoperative transmigration of the wrap (8 %) compared to those that underwent complete mobilization of the esophagus (30 %). Hence, it is now recommended not to extensively mobilize the intra-abdominal esophagus and not to divide the phrenoesophageal membrane (Fig. 43.2) [27].

It has been suggested that patients with esophageal dysmotility, including infants with EA/TEF, will benefit from a partial wrap, thus decreasing the risk of postoperative dysphagia secondary to distal esophageal obstruction created by the wrap in the face of inadequate esophageal motility [7]. Many surgeons prefer a partial, usually anterior, fundoplication via a laparoscopic or open approach in babies requiring fundoplication after EA/TEF repair. At our institution, these patients undergo a laparoscopic Thal fundoplication.

Laparoscopic Thal Fundoplication

The infant is placed at the foot of the operating table and positioned in the frog-leg position. A nasogastric tube (NGT) should be inserted to

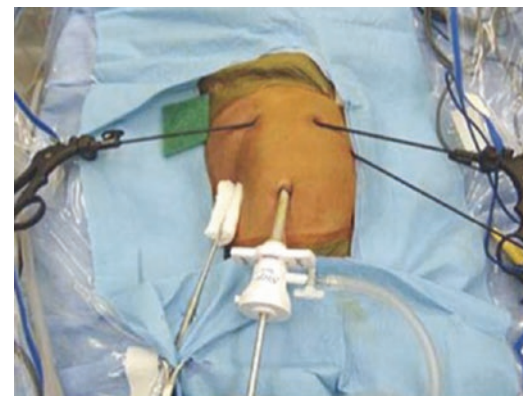

Fig. 43.2 This photograph depicts the placement of the umbilical cannula for the operating telescope and 3 mm instruments through stab incisions for a laparoscopic fundoplication

decompress the stomach prior to beginning the procedure. If a gastrostomy button is present, we remove it prior to prepping the abdomen. After prepping, we place a small piece of gauze and a Tegaderm (3M, Maplewood, Minn) over the gastrostomy site, and the patient is draped in the standard fashion.

A 5 mm cannula is inserted through the umbilicus for a 45° telescope. A 3 mm liver retractor is introduced in the right upper/mid-abdomen to retract the liver anteriorly. Atraumatic 3 mm instruments are placed in the right lateral epigastrium and left lower epigastrium for retraction and dissection. Generally, a 3 mm Maryland dissector is positioned in the left upper epigastrium (Fig. 43.3). Regarding incisions, we employ the transabdominal stab incision technique whenever possible in which only one cannula is utilized in the umbilicus [28].

The operation is begun using electrocautery to divide the short gastric vessels along the upper one-third of the length of the greater curvature. The left diaphragmatic crus is identified followed by the creation of a small retroesophageal window using blunt dissection, with care taken to not disrupt the phrenoesophageal membrane. Attention is then turned to the gastrohepatic ligament, which is divided with electrocautery. The right diaphragmatic crus is now identified, and the small retroesophageal window that was begun on the left side is completed using electrocautery and blunt dissection. Again, it is important not to disrupt the phrenoesophageal membrane during this portion of the procedure. Once the retroesophageal window has been created, if a hiatal hernia is found, the esophagus can be brought into the abdomen and the crura reapproximated with a 2-0 silk suture, incorporating a small portion of the posterior wall of the esophagus.

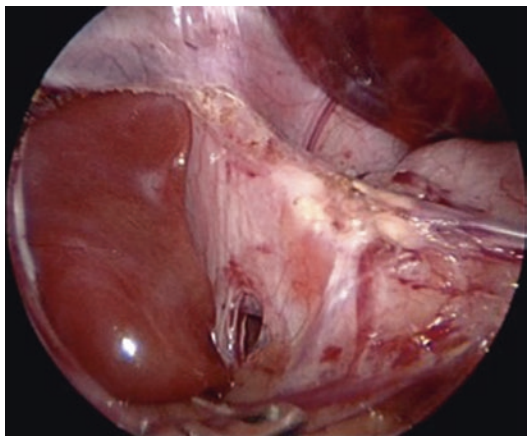

Fig. 43.3 The dissection of the posterior esophageal window is complete. Note the phrenoesophageal membrane has not been disrupted. The esophagus has been gently mobilized into the abdomen, and the crura are ready to be reapproximated posterior to the esophagus

Attention is now turned to creating the anterior fundoplication. An adequate anterior fundoplication should encompass at least 270° of the esophagus. A Thal fundoplication is initiated at the angle of His where the greater curve of the stomach is sewn to the left posterolateral aspect of the esophagus. We use 2-0 silk suture for this approximation, but any nonabsorbable suture can be used. Sequential interrupted sutures are then placed from the greater curve of the stomach progressing up the posterolateral esophagus, until the left crural-esophageal junction is reached. Generally, only three or four interrupted sutures will be needed to create the left side of the fundoplication (Fig. 43.4a). Sewing the fundus of the stomach to the anterior esophagus and diaphragm using interrupted sutures creates the anterior aspect of the fundoplication. The suture line should be performed in a manner that would follow a reverse C (Fig. 43.4b).

The right side of the fundoplication is formed by continuing to sew the fundus of the stomach to the right posterolateral esophagus using interrupted sutures, until the esophageal-gastric interface is reached (Fig. 43.4c).

Regarding other fundoplication options, it is reasonable to perform a “floppy” laparoscopic Nissen fundoplication. The technique for laparoscopic Nissen fundoplication has been extensively described and will not be reiterated here. Many infants who require a fundoplication will also require assistance with enteral feeding due to poor oral intake. When a gastrostomy is needed, we perform a laparoscopic gastrostomy as initially described by Georgeson [29].

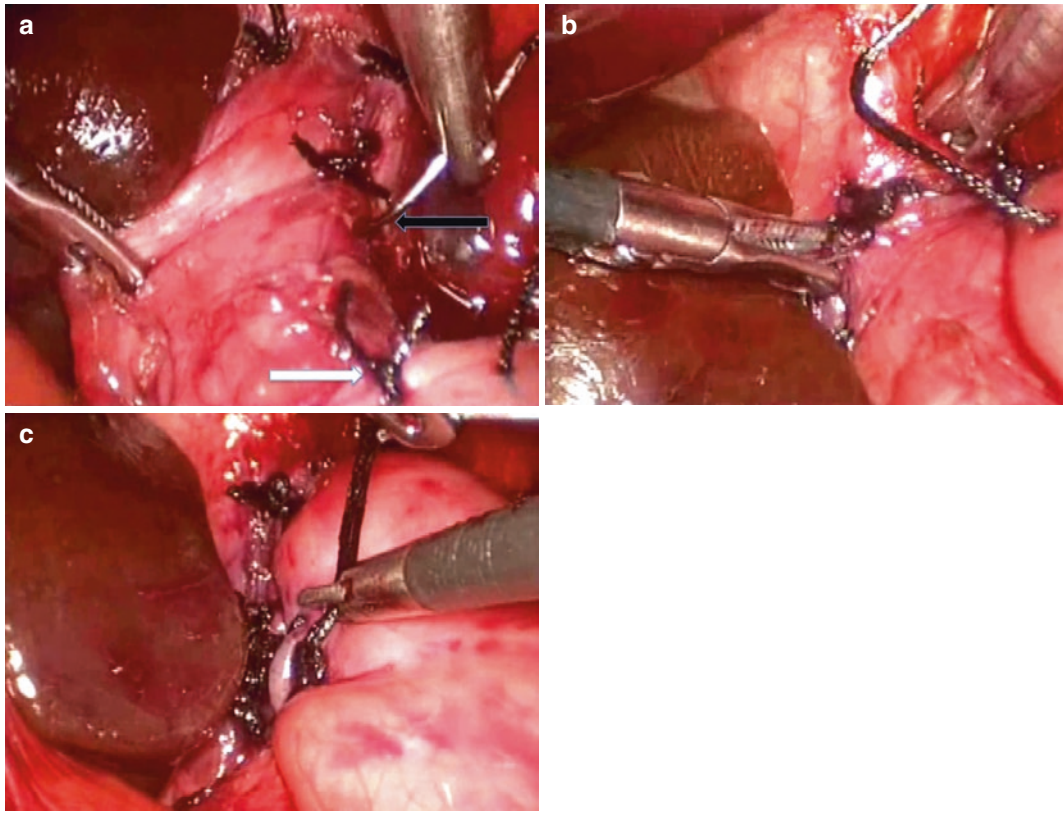

Fig. 43.4 The left side of the Thal fundoplication is being created using interrupted sutures that approximate the greater curve of the stomach to the left posterolateral esophagus from the angle of His (*white arrow*) to the diaphragmatic hiatus (*black arrow*) (**a**). Esophagocrural sutures have been placed to aid in the prevention of wrap migration. In the center (**b**), the anterior portion of the fundoplication has been created by sewing the anterior fundus to the anterior esophagus and diaphragm using interrupted sutures. On the right (**c**), the right side of the fundoplication is being completed. The interrupted sutures are placed from the fundus to the right posterolateral aspect of the esophagus

Outcomes/Complications

In a recent experience at our hospital with 99 patients undergoing both open repair and thoracoscopic repair of EA/TEF, 26 (26%) required fundoplication. All patients underwent an anterior Thal procedure via either an open or laparoscopic approach, and all patients had improvement in their GERD symptoms.

It has been shown that patients undergoing laparoscopic fundoplication have comparable results to the open operation and have a shorter hospital stay. The anti-reflux medications can generally be stopped within 1 month. The most common complications associated with fundoplication post EA/TEF repair are bloating, retching, dysphagia, atelectasis, pneumonia, and wound infection. Late complications include bowel obstruction, wrap failure, and herniation of the wrap [7, 15].

When seen, boating or retching usually occurs shortly after the fundoplication. Unless the infant has an associated neurologic disorder, these symptoms are often related to gas bloat. Dysphagia is more commonly associated with a complete fundoplication and is rarely seen with a partial anterior fundoplication. The concern regarding esophageal dysmotility and subsequent dysphagia in these EA patients is the most common reason many surgeons prefer a partial fundoplication to a complete fundoplication. Wrap dehiscence or migration generally occurs later

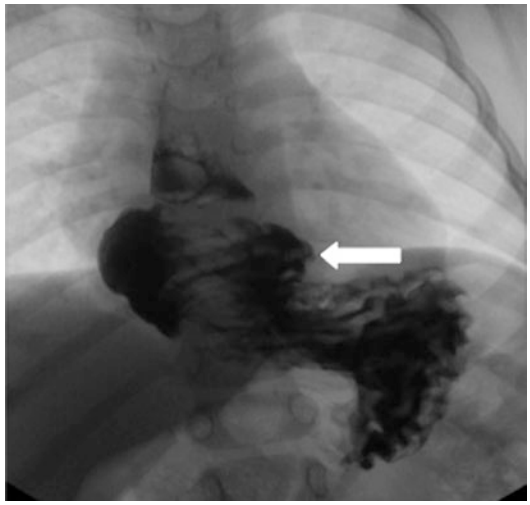

Fig. 43.5 This upper gastrointestinal contrast study reveals a fundoplication that has migrated through the esophageal hiatus (*white arrow*), resulting in recurrent GERD symptoms

and will present with recurrent GERD symptoms or new onset of retching. Upper gastrointestinal contrast evaluation should be obtained and will provide the critical information about the integrity or location of the wrap (Fig. 43.5). As noted, minimal esophageal mobilization will significantly decrease this risk of wrap migration.

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The Stomach and Esophageal Atresia Repair

44

Khalid M. Khan

Introduction

Esophageal atresia (EA) with or without a tracheoesophageal fistula (TEF) is an abnormality of embryologic differentiation. There are a range of phenotypes, and EA-TEF is associated with developmental anomalies in other organ systems. The gastric cavity is intimately related to the esophagus anatomically and functionally. In clinical practice gastric morphological anomalies are not reported in patients with EA, and there is little discussion on gastric function. In this chapter we examine clinical and experimental data that includes the stomach in patients with EA. Gastric neuromuscular development during embryogenesis, electrophysiology, and gastric function after EA repair are reviewed in relation to EA-TEF and EA without TEF. The effects of EA repair surgery and fundoplication on gastric function are examined and whether there is an impact of this on long-term outcome of patients with EA.

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Embryology

The relationship between the esophagus and stomach is an example of the coordinated function that characterizes the alimentary tract. The smooth sequential movement of the upper intestinal tract is made possible by their common origins. The embryology of the foregut is discussed elsewhere in this book. In brief the primitive foregut gives rise to the pharynx, respiratory tract, esophagus, stomach, and proximal duodenum. Differentiation of the stomach commences around 7 weeks of gestation. The gastric cavity and esophagus therefore develop in concert during embryologic differentiation of the foregut. While the precise event or sequence of events that lead to the various EA defects is not defined, there is data that shows anomalies of the sonic hedgehog and related signaling pathways are involved [1]. The same pathways are involved anatomically and functionally in the normal foregut [2]. Furthermore atretic malformation of segments of the alimentary tract distal to the stomach is associated with the EA-TEF spectrum [3].

Gastric Anatomy at Birth

During fetal growth functional maturity of the alimentary tract involves the flow of amniotic fluid, and in utero foregut obstruction leads to abnormalities of fluid volume [4]. The most

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common form of EA comprises a blind-ending upper esophageal pouch and a TEF to the lower esophageal end so that fluid can flow via the tracheal fistula into the distal esophagus and therefore the remainder of the alimentary tract. In EA without a TEF to the distal esophageal pouch, amniotic fluid cannot flow through to the lower esophagus and stomach, and therefore development of the stomach can potentially be affected in such cases. Indeed diminished or absence of air in the stomach is a radiological feature for the diagnosis of pure EA [5].

Sase et al. examined fetal gastric volume using ultrasound [6]. Women with normal singleton pregnancies between 18 and 39 weeks of gestation were included in their study. Gastric measurements were also performed in 13 fetuses with digestive tract obstruction. While the cases of EA were not defined in terms of the presence or absence of a fistula, the gastric area ratio was below the 95 % confidence interval for the predicted value in all five fetuses with EA and greater than the 95 % confidence interval for the predicted value in 7 of 8 with duodenal atresia or distal intestinal tract obstruction. While it is reasonably assumed that amniotic fluid has a role to play in the development of the gut, there has been no systematic study on the development of the stomach and gastric anatomy in patients with EA. Indirect evidence comes from an investigation of the neurohistopathology of the lower esophagus, gastroesophageal junction, and gastric cardia associated with EA. Nakazato et al. used a microdissection technique to study the upper gastrointestinal tract of five patients with EA-TEF prior to surgical repair [7]. A looser than normal Auerbach's plexus configuration was present in the distal esophagus, and the nerve plexus was abnormal in the gastric fundus of all the patients. The authors concluded that the findings suggest the existence of congenital functional impairment of the upper gastrointestinal tract in patients with EA-TEF, due to abnormal development of the myenteric plexus. In contrast to this, a report in which the authors utilized a manometric approach to examine the lower esophageal sphincter (LES) prior to EA repair showed that the relaxation of the LES was normal in response to contractions in the upper esophageal pouch suggesting that the neurophysiology of the gastroesophageal junction is normal in these patients [8, 9]. Our series of patients comprises the largest group of EA patients without a distal TEF undergoing primary EA repair [10]. We have also noted that in cases of pure EA where there is almost no discernible length to the distal esophageal pouch (Fig. 44.1), the LES can still be visualized as a distinct structure (Fig. 44.2). Furthermore we have assessed the stomach visually and with contrast to define gastric anatomy and noted that the dimensions of the gastric cavity have not been compromised in typical cases of EA without a distal TEF (Fig. 44.3) [10]. Conversely a report on nine babies with pure EA, albeit over a decade ago, noted that after initiation of gastrostomy feeds, seven (78 %) developed gastric complications, including two posterior gastric perforations (one fatal). The authors proposed that the high complication rate was due to a small, abnormal stomach that was vulnerable to damage by operative trauma and the effects of handling large volumes of feed. They hypothesized that the stomach is abnormal because it has not been exposed to the maturing effects of amniotic fluid in utero [11].

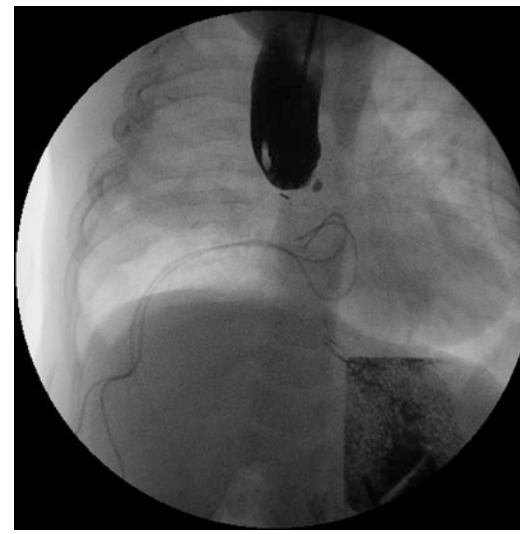

Fig. 44.1 An extremely short lower esophageal remnant that cannot be easily seen even when a probe is used to distend the area of the stomach in a case of pure esophageal atresia. The gastric volume is not diminished

Gastric Electrophysiology

The electrical activity of the stomach was first defined almost a century ago. There is a consistent pattern whether recorded from the serosal or mucosal surface of the stomach or the skin surface [12]. The characteristic electrical activity comprises slow waves of three cycles per minute (cpm) or 0.05 Hz. This is driven by pacemaker cells high on the greater curvature and is an inherent property of the smooth muscle of the stomach and related to cell membrane permeability changes and movement of sodium – interstitial cells of Cajal have been defined as the primary pace setting cells of the gastrointestinal tract [13]. Spikes waves correspond to action potentials of muscular contractions. A maturation pattern of the gastric electrical activity has been demonstrated dependent on the gestational age; a normal electrical rhythm can be detected during early gestation [14, 15]. Chen and McCallum reported that normal slow-wave frequency in the EGG was related to normal gastric motility and that abnormal slow-wave frequencies were associated with motility disorders [16]. Dysrhythmias have been reported in patients with pseudo-obstructive disorders with associated gastric dysfunction suggesting that disordered gastric electrical activity is a sign of intrinsic neuropathic disorders of the gut [3]. Surface skin recording or electrogastrography (EGG) and its uses in clinical practice are discussed in detail elsewhere in this book. Patients with EA have been studied using this technique. In a study of 16 EA patients in comparison to controls, the authors found a wide frequency distribution with two individuals showing tachygastria (frequency ≥5 cpm) and another two demonstrating bradygastria (frequency <2 cpm) [12]. The authors postulated that the wide range suggests that there is an electromechanical dissociation that results in abnormal gastric contractions. In a similar study by Yagi et al., 13 children with a history of EA repair underwent EGG, 5 of whom demonstrated abnormalities [17]. The dysrhythmias continued in the postprandial period and were persistent in 3 of 5. The authors concluded from this that there must be a congenital neuronal defect associated with these findings in patients with EA. In support of this hypothesis, there is evidence to show that the smooth muscle cells of the stomach can exhibit an abnormal slow-wave frequency after inhibition of cholinergic activity [18]. Gastric dysrhythmias are suggested to cause antral dysmotility by inhibiting the strength of

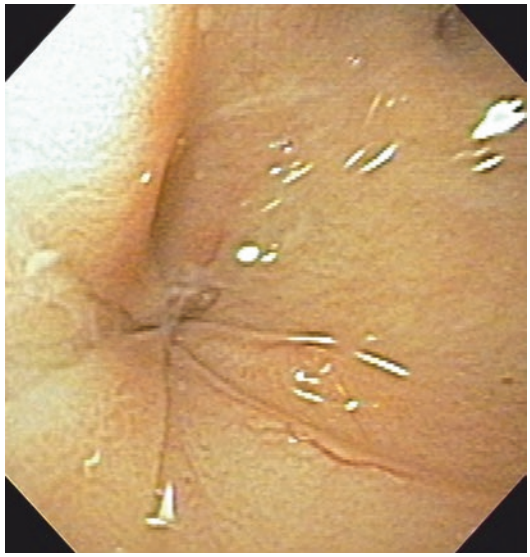

Fig. 44.2 The appearance of the lower esophageal sphincter in the case from Fig. 44.1

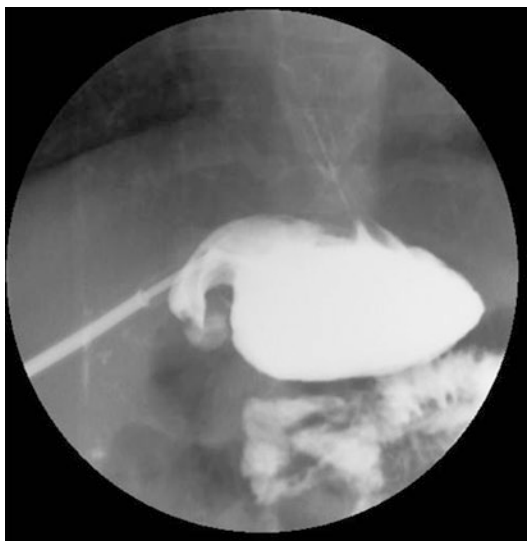

Fig. 44.3 Contrast study after esophageal atresia repair and fundoplication in a case of pure esophageal atresia; the gastric volume does not appear to be diminished

contractions or reducing aboral propagation of contractions [19]. In a study by Bokay et al., there was a significant increase in bradygastria and decrease in tachygastria in the postprandial from the preprandial period in patients with a history of EA repair in comparison to controls [20]. Abnormal EEG patterns were present in 11 of 15 of the EA patients, while in 12 of 15 some clinical evidence of gastroesophageal reflux (GER) had been noted, and 60 % of the EA patients showed reflux on esophageal pH monitoring. There was no difference in the distribution of gastric myoelectrical activity between those with and without esophageal reflux on pH monitoring either before or after a meal. The authors of this study hypothesized that the significant increase in bradygastria and decrease in tachygastria in the postprandial period indicate that the myoelectrical response to ingested meals is sluggish [20]. The lack of a relationship between symptoms and abnormal myoelectrical activity evident in this study was a feature of the studies of Cheng et al. and Yagi et al. In particular there is no clear association between the presence of GER and abnormalities of gastric slow waves from these studies.

Gastric Function

There are limited data on the mechanical function of the stomach after EA repair. Investigators have focused on the stomach mainly to try and explain upper digestive symptoms that are reported in patients after EA repair in children and adults [21]. Gastric emptying by scintigraphy is the gold standard for the study of gastric function [21, 22]. It was first described by Griffith et al. in 1966 and is now used routinely in adult and pediatric patients to assess gastric emptying of solids and liquids [22]. Jolly et al. used scintigraphy to assess liquid-phase gastric emptying as well as GER in children after EA repair [3]. The authors noted that gastric emptying delay and GER were related to the use of tension on the esophageal ends in achieving primary EA repair. In a study by Montgomery et al. using a mixed meal comprising of pancakes in older children gastric emptying was abnormal in two of ten children with GER [23]. Romeo et al. examined gastric emptying in patients who had EA repair in childhood, 60 % of whom had symptoms of dyspepsia and dysphagia [24]. They found longer gastric emptying times in EA patients compared to controls with overt gastric delay in 4 of 11 patients using solid-phase emptying. The authors concluded that delayed gastric emptying is common and may be responsible for GER in EA patients. Our own data (unpublished) has been based on long-gap EA patients [10]. We examined liquid-phase gastric emptying in nine infants with only one showing delay (gastric emptying half-life – T ½ of >90 min); all our patients had undergone a fundoplication. In the most recent publication on the subject by Caldaro et al., 12 of 39 patients with EA exhibited delayed gastric emptying [25]. The possibility of gastric emptying delay as a cause of significant GER though elegant is not clear from the pediatric data. In a study by Aktas et al., gastric emptying times did correlate with the degree of scintigraphically assessed GER in infants [26]. In children with severe neurological injury from birth (cerebral palsy), gastric emptying times were found to be the same in patients with pathological GER diagnosed with pH monitoring and control patients [27]. Gastric emptying, foregut dysmotility, and GER often coexist. This has been noted in specific patient groups such as the abovementioned children with neurological injury [28], as part of morphological syndromes and foregut anatomical disorders. Manometric study of gastric motility in EA patients was conducted by Romeo et al. in the study of EA patients discussed above [24]. The investigators were able to recognize the features of the migrating motor complex in the interdigestive phases: phase I, a quiescent period; phase II consisted of irregular motor activity; and phase III a period of coordinated contraction. Three peristaltic wave types (I, II, and III) cycle were also identified. In 5 of 11 patients, the duration of the third phase and the frequency and amplitude of the peristaltic waves were abnormal. The authors found that antral hypomotility was due to increased duration of the third fasting phase and to reduced amplitude of type III

peristaltic waves. The significance of the findings was less clear in that two patients with GER were symptomatic and had delayed gastric emptying and abnormal gastric manometry, two others with delayed gastric emptying and abnormal manometry had no symptoms, and one patient had manometric abnormality but without major symptoms or gastric emptying problems. The authors noted that the alterations observed had some similarities with those observed in patients with primary or secondary dyspeptic syndromes. As noted above antral dysmotility may be a feature abnormal slow-wave activity [20, 29]. It could be postulated that foregut dysmotility gives rise to gastric emptying delay which in turn results in GER. In addition primary repair of EA could potentially involve disruption of the vagus nerve further complicating the etiological relationship between electrophysiology, manometry, and symptomatology in these patients [30].

Fundoplication

Gastroesophageal reflux is a common sequel to congenital disorders of the foregut. In one study almost all patients treated for EA developed GER [31]. Not surprisingly therefore most case series of EA patients show that a proportion of children undergo fundoplication [32]. Fundoplication in children with preexisting upper gastrointestinal dysmotility may however be problematic. In a series of children evaluated for symptoms of upper gastrointestinal motor dysfunction having undergone fundoplication for severe GER symptoms were unchanged or worsened after fundoplication [33]. The outcome of fundoplication may be specifically related to gastric motility. Loots et al. examined dysphagia after fundoplication and found that children who developed postoperative dysphagia were those with preoperative gastric emptying delay as compared to children without gastric emptying problems [34]. Conversely mean gastric emptying time was shown to be reduced in patients after undergoing Nissen fundoplication [35]. The acceleration in gastric emptying after fundoplication was elaborated to represent a shift toward normal gastric emptying times in the vast majority of patients in one study [36]. This would imply that while post-fundoplication symptoms may develop in patients with preoperative gastric emptying delay, ultimately gastric emptying may be improved in this group. The findings in relation to post-fundoplication gastric emptying are however not consistent. In a study of children undergoing Nissen fundoplication for GER, the investigators were able to demonstrate reduction in gastric compliance, an increase in minimal gastric distending pressure, exacerbation of the sensation discomfort with gastric distension, and yet no effect on gastric emptying [37].

Patients with EA are likely to need a fundoplication if tension is necessarily applied to the esophageal ends to achieve primary anastomosis [19]. Wheatley et al. described wrap disruption and recurrent reflux in 33 % of a pediatric population treated for EA [38]. The authors theorized that upward tension on the wrap owing to the presence of a shortened esophagus probably predisposed these patients to an increased frequency of fundoplication failure. Snyder et al. also concluded that the same factors responsible for the development of reflux in children with EA (poor acid clearance, altered motility, esophageal shortening) may contribute to the higher failure rate [39]. The authors showed that a complete or Nissen fundoplication failed twice as commonly as partial wrap fundoplication.

Apart from failure of the fundoplication, there are other consequences to a Nissen fundoplication in patients after EA repair. In the study by Curci et al. of 14 of 31 patients who underwent a Nissen fundoplication, dysphagia requiring supplemental gastrostomy feeding became an issue in 5 [32]. Of those five patients, four underwent postoperative manometry and extended pH monitoring, which revealed normal LES pressure, normal pH results, and marked esophageal dysmotility. The authors postulated that the fundoplication created a mechanical obstruction for those patients with a dyskinetic esophagus that cannot generate the pressure to open the LES. Other investigators have also concluded that particularly in children with EA, fundoplication cannot be considered a procedure

without complications and that problems resulting from disturbed gastric and esophageal motility should not be underestimated [40]. As discussed above fundoplication is inevitable in cases of long-gap EA where significant tension is necessary for primary repair, and, as noted by Esposito et al., dysphagia occurs independent of the anti-reflux mechanism adopted and that dysphagia especially when associated with respiratory symptoms may be a consequence of the primary dysmotility of the esophagus that typifies EA [41]. In our true long-gap EA patients, fundoplication was always performed after EA repair, and we have shown that the children are able to develop normal feeding milestones [42].

Long-Term Outcome

The most commonly reported long-term problem after EA repair is GER [43–48]. An Australian long-term follow-up study showed that older symptomatic patients had a high risk of complications: 63 % had reflux symptoms and 19 % had severe symptoms [43]. Another long-term study of 227 EA patients, spanning more than two decades, found GER in 127 patients (58 %); 56 patients (44 %) required an anti-reflux procedure [49]. Similarly in a series of 31 EA patients treated for GER 14 patients (45 %) required a Nissen fundoplication [32]. A study of adults found that GER was a common problem that impaired quality of life in 30 % of patients [44]. Tovar et al. showed symptoms were related to reduced acid clearance as a result of ineffective peristalsis in the distal esophagus in relation to GER [45], and as discussed above disordered esophageal motility is known to be a constant feature of the repaired esophagus in EA and therefore poor esophageal clearance [43–50]. Apart from low LES pressure and lack of propagating motility, esophageal contractions are simultaneous and weak, especially in the lower esophagus [20, 50, 51]. Low LES pressure in such patients has been associated with more severe reflux and aspiration pneumonia [52]. However, no correlation was found between pulmonary problems and the presence of GER, esophagitis, or esophageal dysfunction [49, 53].

Summary

The available data on gastric pathophysiology in the setting of EA is limited but does allow some conclusions to be drawn. It can be reasonably argued that the foregut neurophysiology may not be normal at birth at least in a proportion of EA patients; however, the genetic data which is largely based on animal models does not allow us to differentiate between the known human phenotypes. At birth the morphology of the stomach is not greatly altered in EA-TEF, and there is insufficient data to suggest gastric volume is reduced in cases of EA without TEF. Gastric emptying delay can be a problem in patients and may contribute to GER. The etiology of gastric delay may involve antral hypomotility related to congenital neuronal disruption in some patients. The effect of EA surgery and possible injury to the vagus nerve can be considered as contributing to gastric emptying delay. Tension applied to the esophagus affects the gastric cardia, and fundoplication is known to have an effect on gastric physiology though how this affects patients with EA is less clear. Our own findings based on long-gap EA patients along with other data indicate that indeed a small proportion of children consistently demonstrate abnormalities of gastric function; however, this does not account for the proportion of patients with a history of EA-TEF repair that expresses upper gastrointestinal symptoms. Apart from GER there is evidence to show that the upper digestive and pulmonic symptomatology is related to poor clearance from the esophagus and may be the major factor to consider in adults who present with esophagopulmonic symptoms.

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45 Learning to Eat After Esophageal Atresia Repair: In Infancy and Childhood

James Brudney

Once the esophagus has been surgically connected, the next steps in the progression for the child to eat orally begin. Focusing on eating will be the charge of the speech therapist, a specialist with extensive knowledge and experience dealing with feeding difficulties in infants and children. The therapist brings an understanding of the swallow mechanism, feeding skill development, and infant/child development to the therapy process. He will lend his expertise to the well-being of the child to develop the most carefully planned feeding program. The child and parents are at the center of this program, which combines the child's past experiences, the parents' beliefs and expectations, and following the child's lead. The therapist melds these components with his own knowledge to visualize a course with the desired outcome of eating. The course is determined by information gathered in the evaluation, knowledge of normal feeding development, and understanding how the repair process interferes with the normal development of the child. Three primary areas are examined in the evaluation to identify where the child is starting on the spectrum of developmental feeding skills. The areas include oral motor skills [1–5], sensory integration [6, 7], and physiological function. Throughout the course of treatment, there will be many questions raised by the parents, and the quality of the answers will influence the treatment outcome. Their buy-in to therapy is mandatory for success. Education and participation of parents in the therapy program will help address many questions such as: will my child ever eat? How long will it take my child to learn to eat? Parents base so much hope upon the initial answers to these two questions. The therapist's responses to these questions can set the entire tone for the duration of treatment. Many therapists would acknowledge that working with children after repair of esophageal atresia presents the most challenging collection of issues related to eating for the speech therapist.

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Normal Development

Understanding the normal feeding development in newborns and their progression of skills from birth to toddler-hood is crucial for the feeding therapist [1–5]. The therapist's decisions should be guided by reference points like child's skills, the understanding what is expected and what are red flags and what skills are to develop next. A newborn baby begins life with certain "prefeeding" reflexes of rooting, sucking, and swallowing. These reflexes emerge around 28 weeks' gestation. At 34–36 weeks' gestation, the fetus begins to coordinate a rhythmic

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suck-swallow-breathe pattern in anticipation of feeding moments after birth. The first month of life is about eating and gaining weight to sustain life, using the pre-wired reflexes in response to repeated bodily cues, classic conditional learning. For example, say, an infant performs 50–75 SSB cycles while eating 2 oz of milk each feeding eight times daily. That works out to 400–600 cycles/day and 12,000–18,000 cycles the first month. That is a staggering amount of practice in the first month of life. Chances are the baby will be eating more than 2 oz at the end of the month. In months 2 through 6, the infant refines the suck-swallow-breathe pattern to accommodate numerous changes occurring during this period including increase in oral secretions, integration of the sucking reflex where sucking becomes an intentional act, and reabsorption of the fat pads in the cheeks creating more space orally. From 7 to 12 months, the gag reflex is less strong as more textures are introduced, and tooth eruption gives the infant new sensory receptors. Alternate feeding positions (being more upright), adapting to spoon presentations of puree consistency, and the emergence of independent feeding behaviors increases as the child transitions to more mature eating skills.

During the second year of life, many gross motor and fine motor advances facilitate increased eating independence [8, 9]. Thoracic stability and head control are stronger allowing the child to use his arms and hands more effectively to reach for items and explore them orally through the many sensory receptors of the mouth and hands. A controlled bite on soft solids appears mixed with a phasic bite and sucking marking the development of cerebellar control through graded movements. Simultaneously, food consistencies expand with hard and soft solids, thicker puree, and mixed textures leading to growing oral motor control and sensory tolerance. Their diet repertoire is transforming, and soon they will be sharing the same food choices as their parents. Appreciating the skills and developmental changes a typical child encounters across the first 24 months of life magnifies the challenges which lie ahead for child with esophageal atresia.

Realities of Repair

Medical intervention for esophageal atresia children is very intrusive on the child's overall development, especially feeding skills. The hospitalization sets the child up for delays with so many skills by the time they leave the hospital connected and ready to return home. Discharge from the hospital varies greatly depending upon type of repair. A primary repair of the esophagus implies one surgery to connect the two ends of the esophagus. Recovery is usually short, and feeding therapy proceeds over the next several months as weaning from tube feedings encourages hunger cues and motivation to eat. A two-stage repair will prolong the process by weeks because of the additional procedures and time needed to prepare the esophageal ends for attachment [10]. In the intermediate procedures, traction on the ends of the esophagus is placed to promote growth. During this time, the child is sedated and paralyzed to prevent complications. This down time disrupts a critical point of development for early sensory skills, oral motor skills, and learning opportunities from daily routines. The child misses out on how to manage one's environment when stressors are encountered, responds to stressors in inappropriate manners, and cultivates incorrect associations with typical newborn stimuli. Stressors present before repair include frequent oral suctioning to manage oral secretions which are not removed by the nasal catheter which courses down into the blind upper esophageal pouch. The noise of the suction and tape on the face to secure the catheter are noxious irritants to the child. After repair, the child is weaning from narcotics making them more irritable, the gut is slow to wake up after surgery, and the persistent intrusion of caregivers visually puts the child in a defensive demeanor. Oral aversion is a frequent end result of the medical intervention shown by the refusal of the child to all stimuli near the face, mouth, or lips and an extreme behavioral response characterized by gagging, crying, fighting to turn away, blocking with hands to avoid the presentation or approach. In the course of recovery, the healing process in the esophagus causes strictures and scarring which narrow the inner diameter of the esophagus and prevent movement

through the tube. Compounding the narrowing is the lack of peristalsis along the esophagus. Gravity becomes the source of motion. Dilatations break down the scarring tissue and expand the opening of the tube, but with a price. The child is intubated each time and reinforces the established negative associations during a time when therapy is attempting to establish new, positive oral associations. The dilatations are necessary for the long-term function of eating. In addition, feeding tube schedules diminish hunger cycles, and missed opportunities to foster sensory integration through holding and swaddling add to the harsh environment. However, experience amassed over 13 years of treating children with long-gap esophageal atresia (5 cm and greater in length) and with short-gap atresia has shown that therapy can directly change the development of these children. They can learn positive oral experiences, learn to manage their environmental stressors with appropriate responses, and learn to eat. The path will be different from typically developing children, but the outcome is expected to closely align with their peers. There has been recent validation of these expectations from a longitudinal study looking at the eating skills of 40 long-gap children after repair compared with a control group of like peers typically developing [11]. The study concluded that the long-gap children catch up to their peers with eating skills without significant limitations.

Approaches for Treatment

No single approach or method has been proven to be the most effective with all children in helping them to learn how to eat after repair for esophageal atresia. So many variables play into the decisions regarding approaches to take with each child. Many of the variables have been previously discussed in the chapter, related to the perspective of the child, the parents, the medical history, and the course of intervention and duration. Often times a combination of strategies from different methods may benefit the child, forming the crux of the program for the child. A popular method of feeding therapy used with children 15 months and older is the Sequential Oral Sensory feeding program created by Dr. Kay Toomey, a psychologist [12]. This approach is helpful in addressing many different feeding problems. The Sequential Oral Sensory (SOS) feeding program is a noninvasive developmental approach to feeding. It focuses on increasing a child's comfort level exploring and learning about the different properties of foods, including texture, smell, taste, and consistency. The SOS approach allows a child to interact with food in a playful, non-stressful way. It follows the steps to eating, beginning with the basic ability to tolerate food in the room, in front of the child, touching, and eventually tasting and eating foods. Parent education and involvement is an important part of this feeding approach [13–14]. A therapist works directly with the parents while they are watching each feeding session to learn this approach to feeding. Parents learn to identify physical signs and "body language" to identify when the child is overstimulated and to assist with setting up the home program.

A case in point, I worked with a 4-year-old girl status post long-gap esophageal atresia repair that came to the initial evaluation and sat at the table to discuss what we would do during her visit. Stating she was OK with the process, I began to prepare the space to explore some sample foods to see what kind of skills she possessed and where were the barriers or walls that kept her from eating. At the sight of seeing foods which were outside of her comfort zone (i.e., yellow, white, or light orange), she began to gag and wretch and vomit tube feedings. Once the food was removed from sight, then she was able to calm herself. Her defenses were so high that the sight of food made her exhibit severe negative behaviors. Over the course of 6 weeks in intensive therapy (2–3 visits weekly for 45–60 min sessions), the girl learned to make positive associations with food, not see it as threatening and could begin to respond to her own cues of hunger and pleasure with food. Parents were intimately a part of therapy, participating in the program at therapy and then repeating the episodes with food at home to generalize skills for the girl across setting. She is an example of an extreme case of aversion to eating, but the walls or barriers were very apparent. Any food

which fell outside of her repertoire of "safe" foods was considered threatening and triggered such an extremely inappropriate response that set her back for progressing with eating. When she began to learn that all foods were safe, she could begin to explore them in different ways, the walls came down, and the eating increased over time. After 3–4 months of continuing the treatment program at home with family, the girl was able to get the g-tube removed and continues to eat a typical adolescent diet with no limitations or restrictions.

A preferred method for infants involves a natural learning technique in which the therapist facilitates learning through the typical environmental stimuli from the caregivers and expected development. Reinforcement is provided to the child along with the cues and opportunities which will elicit the reflexive responses expected from their developmental age. For example, the rooting reflex in a 3-month-old infant can be a helpful response to incorporate into therapy as a way to increase sucking behavior after prolonged intubation in a 3-month-old male infant. Therapy can build off this reflex to set in motion providing positive oral experiences. As an infant, their long-term memory is not established, and new experience can become their new history. In contrast, an 8-month-old female infant with prolonged intubation needs a different strategy. The root reflex has been integrated, and sucking may not provide any interest to her. A different strategy is taken based upon what this child demonstrates in oral skills and defensive behaviors. Perhaps she will bring toys to her mouth and bite on them and explore them lingually, but she will not let others present anything to her face, refusing to accept touch or even kisses from her mother, let alone food in her mouth. Identifying the starting point of treatment helps the therapist lay out a "road map" of sorts for the parents to follow and bridge their understanding of what the child will need to reach the goal to eat.

Evaluation

The involvement of speech therapy begins when the major medical issues have been resolved following repair. The child is evaluated by the speech therapist and focuses on three primary areas of concern, involving oral motor skills, sensory integration skills, and physiological function. Findings from these three areas create the foundation for the child's therapy program. The evaluation may originate with any one of the three areas, often decided by how the child initially responds to the new therapist approaching. If the child cries, fusses, or turns away upon approach, these could signal fear which often indicates a lack of trust. Without trust in the caregivers, the child will always shut down, and therapy will fail. Trust building can start with providing positive interactions with the child, such as swaddling, rocking, or hand and foot massage. Success with these calming strategies can be passed onto parents and staff to provide additional positive interactions outside of therapy. The multiplicity of procedures and interventions to repair the child's anatomy come at a cost to their internal state regulation or sensory integration.

Most children are bombarded with repeated aversive stimulation for which they generate misaligned or inappropriate responses. Aversive stimulation can range from lying on the back in extension without boundaries and oral suctioning to feeding tubes and oxygen lines taped across the face, to IV lines and boards taped on the arm. These necessary actions occur at a critical period of learning for the child and result in misinterpreted signals and an inappropriate response. During assessment, the therapist is watching how the child is coping in their current environment. If doing poorly, the therapist needs to try some strategy to bring about improvement in the child's internal state control. Some strategies may include turning lights off, using quiet talking, and providing confinement or boundaries with swaddling, blanket rolls, or side lying. Changes in the child are noted by quiet breathing, increased sucking, less fussing, closing eyes, and overall less fidgeting. With these changes, the therapist may move to elicit nonnutritive sucking to create improved state regulation.

For example, a 3-month-old female has been held infrequently on a pillow throughout her hospitalization due to multiple lines, tubes, and cords attached to her body, and parents have

been scared to hold her since she always cries or screams when she is moved. Being held is normally a preferred activity that infants respond to with cooing, calming, and falling asleep. In this case, her response to the stimulation, even her interpretation of what's happening, is inappropriate. To help her learn new responses and improve her appraisal of what caregivers are providing, she needs positive nurturing interactions. These events will encourage trust building through the calming and comforting experiences. Swaddling is an ideal strategy to initiate with this infant during therapy. In addition, less crying eases the parents' apprehension with holding her and raises their comfort and confidence level with their child. As trust builds, the child reduces her resistance and engages in more activities. Internal self-regulation strategies are valuable to getting performance from the child. These strategies can be adjusted for the older child based upon developmental levels. Occupational therapists are a great resource for learning more about the techniques on sensory integration.

Achieving some state regulation is critical to progressing to the second important area, oral motor skills. Assessing oral motor skills examines the basic anatomy of the face, cheeks, lips, tongue, and palate along with complexity of muscle tone, range of movement patterns, timing of movements across the structures, respiratory coordination, and swallowing [13–15]. The therapist looks at the sensory sensitivity of the oral system and how reactions to stimuli affect the ability of the child to manage responses to stimulation. The therapist takes an inventory of the skills demonstrated to identify where the child falls in comparison to his or her age-based peers. Is the child latching and grooving her tongue to a gloved finger or pacifier? Can nonnutritive sucking be elicited and sustained? Can the child take tastes of water or formula from a pacifier or gloved finger? Can the child coordinate suck-swallow-breathe from a bottle? Is the child's breathing pattern prohibiting the child from swallowing? Is the child swallowing safely, showing overt signs of aspiration? These are standard questions in an oral motor assessment for all infants and children. Unfortunately, EA children often give more complicated answers which generate additional questions. Nonetheless, the answers to these questions direct the therapist in their treatment plan. Secondly, they provide a starting point for education to help the parents begin to learn meanings behind the cues from their child. Every child has a different starting point based upon their experiences, behavioral responses, and skills. Interpreting the meaning of these behaviors will provide insight into how we can help them overcome the negative associations, learning a new set of positive experiences with appropriate responses.

While assessing the oral motor skills, the therapist is watching the responses to the interactions. How does the child react with touch to her face and lips? Does she gag, wretch, and drop her saturation level? Is she swallowing her oral secretions effectively or is suctioning needed every 15–20 min by staff? Are the secretions passing through to the stomach? Does she allow massage on her hands or will she grasp and hold onto objects? Will she bring anything to her mouth independently? Is she hypersensitive in her gag with touch to her mouth or with anything that comes near it? Does the child use gagging behavior to escape oral activities? Does the child cry or turn away? Does the child block with their hands any movement toward the face? These types of responses are learned reactions to intrusions that have not been soothing, nurturing, or comforting and have ultimately led to negative associations. With toddlers, these behaviors can be more dramatic and more challenging to overcome.

The third area of importance is the physiological function of the GI system. How does any swallowed liquid or food move through the esophagus into the stomach? Is there any peristalsis seen on the UGI studies? Does the esophagus dilate greater superiorly to the anastomosis site causing blockage and retrograde movement of the bolus? The retrograde movement can present as reflux symptoms clinically and turn the child off from any oral intake. Function refers to the mouth-esophagus-stomach-intestine relationship. What are the signals or messages the child is receiving that would turn him or her off from eating or elicit refusal with easier tasks like tasting drops of water or formula while sucking on a pacifier or gloved finger,

swallowing secretions. If the body is saying, "don't take any drink, it will make me vomit" or "I'm not hungry, I don't want to drink," then what do these cues or signs look like to the caregiver so that they know when it's not OK to push. Does it mean that when the esophagus is narrowed, the bolus gets stuck at the anastomosis and reflux occurs? Knowing the function of the repaired anatomy gives us information about fluids moving through the tube.

Beneficial information can be obtained from repeated UGI studies showing the surgical site, any narrowing related to scarring, the esophageal function superior and inferior to the anastomosis site. Dilatation procedures occur regularly following connection of the esophagus as a means to reduce and prevent excessive scarring and stricturing of the esophagus. Each time the child has a dilatation, asking how significant the narrowing at the anastomosis may shed light on how the child is reacting to food or drink in therapy. It is therapeutically significant if the dilatation opens the esophageal anastomosis to 10–14 mm every 2 weeks and then is scarred down to an opening of 6–8 mm diameter 2 weeks later. The passage of fluids through the esophagus is greatly reduced and can explain why the child may start out willing to taste formula but then stop after 3–4 swallows, becoming irritable with arching and twisting and crying. The child may resort to nonnutritive sucking (NNS) with a pacifier and resting several minutes. NNS can promote esophageal peristalsis, making the child feel better and interested in trying tastes again. Strictures cause increased gagging with secretions, refusal with all oral tastes, reflux symptoms, and cause the child to shut down in therapy. The function of the anatomy provides more clues and explanations to understand what drives the child's responses. An "ah ha" moments in therapy arise when the child is seen days after dilatation and is more interested in taking tastes of milk without gagging, vomiting, or stopping after 3–4 swallows. Seeing these kinds of changes clinically and knowing the physiological function help the therapist correlate what's happening with the tastes after swallowing. Adjustments are made to the treatment plan accordingly and education continues with the parents about relation of the esophagus and eating.

Therapy

Much of the knowledge and expertise with helping children learn to eat stems from watching their cues, their behavioral responses to the presentations of food and drink [16, 17]. How they react to your requests and what signals their body is giving them arise from knowing the physiological process that is occurring when they swallow the food and the drink that enter the esophagus. Do they turn a certain way, to the right to trigger Sandifer's reflex or arch, or turn red faced and whine, all signs of reflux which we know every child will exhibit as a result of the anomaly of esophageal atresia.

In many ways, the evaluation is similar to a trial run for therapy, finding out what works and what does not work. Therapy sessions become a process of taking steps forward and sometimes back stepping when necessary. The forward steps increase positive experiences with oral activities which will foster the child's curiosity toward greater exploration, facilitate skill development, and synch up natural physiological cues with developmental feeding skills. To this end, the child learns to pursue drink and food from an internal motivation, hunger. Along the way, cognitive connections are made between hunger and food. The session begins with a mini reevaluation to see how the child is tolerating the current level treatment. The session progresses by challenging the child to try more tastes, or new volumes, or different foods without falling apart and resulting in negative responses. The child must direct the therapy through his or her reactions to new presentations. Pushing too hard and too fast will only cause to child to step backward and shut down.

Therapy sessions have another purpose: to teach parents how to create a positive environment around meal time and integrate new skills learned in therapy on a daily basis in the home setting, giving them practice with supervision to carry out sessions at home. The incorporation at home helps the child generalize the new skills and supports learning in more natural settings. At some point in therapy, the child begins to make connections for learning on their own, and the natural learning of skills will take over for the child allowing them to advance without therapy. A skilled therapist is

always asking the question of when is it time to wean treatment and let the child go it alone. Parents are capable of supporting and guiding the child to the next skill level because of their education, their understanding of the skill developmental, their ability to read cues, and their support and belief in the child to succeed.

As the child begins to increase their intake orally, the focus of therapy turns to reduction of g-tube dependence to promote increased hunger. Promoting hunger without sacrificing weight gain is a fine balance since each works against the other causing prolonged dependence on tube feedings. During this critical period of growth for the child, the primary concern is always the growth of the brain and body for overall development, even if it means delaying individual feeding skill development. The first 2 years of life is the window for brain growth and development in the child. Individual skills can still be learned after that time, but the brain is set. Many issues arise with tube feedings. Children will start out with continuous feedings which diminish any hunger and reduce their desire to feed. Progressing to bolus feedings helps put the child on a cycle of hunger and satiation, a typical pattern of infants and children. Bolus feeds are consolidated volumes given over reduced time allowing for periods of nonfeeding. The transition from continuous feeds to bolus feed can take weeks and is driven by the child's tolerance with faster feeds. Once bolus feeds have been achieved, withholding feedings may become a strategy to increase oral feedings, only when the child is doing well on the growth chart. If they are behind, as many EA children are, it will be necessary for the child to get adequate calories for growth and having involvement with a dietitian to monitor adjustments with feeds, formula selection, and growth tracking. These issues will persist beyond the point when therapy is finished and managed by the pediatrician until no longer a concern.

Conclusion

For every therapist working with EA children, there are two difficult questions that will be asked by parents and are nearly impossible to answer accurately. It's important that the therapist is ready to face them when they are raised in conversation. The first question is, will my child learn to eat? It is a crystal ball question with so many variable factoring into the equation. There are some indicators which help in answering, including diagnoses, syndromes associated with the EA, neurological involvement, and overall developmental progression of the child. The more contributions from these variables, the greater the challenge eating becomes. The second question is, how long will it take my child to learn to eat? From experience with numerous EA children repaired, parents are told to expect 6 months to a year after discharge from the hospital to be working on feeding issues and weaning from g-tube feedings. It helps prepare the parents for a long road to recovery yet gives them hope for their child. As discussed earlier in the chapter, feeding a child is the essence of nurturing the child, and when that function is missing, parents question their value as a parent. Restoring that precious value for parents is a bonus therapists receive with guiding the child on the path to eating.

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Part IX

The Airway: Nerves, Malacia and Life-Threatening Events

Apparent Life-Threatening Event (ALTE) in Infants with Esophageal Atresia

46

Francesco Cozzi and Denis A. Cozzi

Introduction

It is to Cameron Haight's credit that he was the first surgeon who successfully accomplished in 1943 a primary esophageal anastomosis in a baby born with an esophageal atresia and a distal tracheoesophageal fistula [2]. Less attention has been devoted to the description by Robert Mercer of the stormy postoperative course of this patient, who on the 12th postoperative day developed recurrent episodes of stridorous respiration coming on during or shortly after feeding. On the 47th postoperative day, one of these episodes was characterized by severe respiratory distress after feeding; the supervening cyanosis was followed by "a respiratory arrest during the expiratory phase." Resuscitation was successfully carried out [4].

Subsequently, many authors have used a variety of terms to describe a similar episode characterized by a respiratory arrest in infants with esophageal atresia (Table 46.1). In 1996, we proposed to call these episodes "apparent life-threatening event" (ALTE) [42]. This term was coined by the members of the National Institutes of Health Consensus Development Conference on Infantile Apnea and Home Monitoring to describe an episode that appears life threatening to the caregiver. These episodes can occur during sleep, wakefulness, or feeding. Gastroesophageal reflux is one of the identifiable conditions that can cause ALTE [11].

After Haight's report, survival rate following primary repair of esophageal atresia has progressively improved, so that today the mortality has been reduced to an insignificant proportion. Improved survival has resulted in an increasing awareness of short- and long-term postoperative complications. ALTE represents one of the most severe complications because in several patients it has progressed to sudden death [15, 21, 25, 26, 34, 37, 38].

We previously described the clinical and physiological manifestations of respiratory distress in infants with esophageal atresia. In this section, 65 years after its first description [18], we will focus attention to our knowledge on ALTE in infants with repaired esophageal atresia.

Pathophysiology

In 1945, Mercer concluded that the syndrome he described was due to an excessive activity of a vagal reflex causing "a laryngeal spasm and a cardiac and respiratory arrest in expiration." In his view the vagal reflex was initiated by stimulation of sensory endings of the pharynx because

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Table 46.1 Various terms used to indicate a sudden and unexpected respiratory arrest in infants with esophageal atresia

Cardiac and respiratory arrest [4]
Respiratory and cardiac depression [20]
Reflex apnea, lifeless attacks [16]
Breath holding spell [15]
Apneas, malaises [25]
Apneic episodes life-threatening anoxic spells [26]
Respiratory arrest [29]
Dying spells [32]
Death attacks [33]
Near miss sudden death [35]
Near fatal events [39]
Apparent life-threatening event (ALTE) [42]

ALTE came on during or shortly after feeding. The possibility that the stridor was due to a congenital anomaly was ruled out because the larynx was normal at laryngoscopy. The possibility that the ALTE was due to anoxia was excluded because of the rapidity with which cardiac and respiratory arrest developed following the onset of laryngeal stridor. Therefore, laryngeal stridor and respiratory arrest in expiration were better explained on the basis of a neurogenic reflex [4].

In 1954, Allen et al. reported clinical observations suggesting that the syndrome of inspiratory laryngeal stridor associated with ALTE described by Mercer in an infant with esophageal atresia may occur also in infants with tracheal stenosis or in otherwise normal infants. In an infant without esophageal atresia, tracheal stenosis was documented by a tracheogram and by a bronchoscopy, which revealed a 50 % reduction of the size of distal tracheal lumen. Tracheal narrowing was considered to be due to a congenital weakness of the tracheal walls, more than to a compression of a left innominate artery arising from a dextroposed aortic arch. Actually, division of the left subclavian artery and suspension of the innominate artery were not followed by relief of symptoms. Allen et al. described also in infants with esophageal atresia an ALTE not associated with inspiratory stridor but observed after a blood transfusion, or after the passage of a string for future esophageal dilatations, or after the introduction of a bronchoscope, or after regurgitation. The conclusion was that in infants with or without esophageal atresia, ALTE with or without inspiratory stridor was due to an overactive vagal reflex [20].

In 1963, Fearon and Shortreed noticed that the clinical manifestations of respiratory distress associated with ALTE of some infants with esophageal atresia were not different from those of some infants with a tracheal compression by various congenital vascular anomalies. They speculated that the respiratory problems were due not only to a neurogenic mechanism but also to tracheal compression between a dilated esophagus posteriorly and an anomalous mediastinal vessel anteriorly. They pointed out that the stridor may be biphasic, that is, both inspiratory and expiratory. The intrathoracic tracheal compression was considered responsible for the airway obstruction in expiration, whereas inspiratory stridor was attributed to an associated laryngomalacia [16].

Actually, patients with a variable obstruction of the thoracic trachea have a greater difficulty in breathing out than in breathing in, because the negative intrathoracic pressure during inspiration tends to enlarge the tracheal lumen, whereas during expiration the positive intrathoracic pressure tends to increase the obstruction. Conversely, patients with a variable obstruction of the upper airway have a greater difficulty in inspiration than in expiration because during the inspiration the atmospheric pressure around the cervical airway exceeds the intratracheal pressure that becomes negative below the obstruction and tends to aspirate the tongue, which may obstruct the pharyngeal and laryngeal airways [3, 22].

Fearon and Shortreed described also what they called "reflex apnea," that is, an ALTE not associated with respiratory distress but initiated by a bulky bolus of food in the esophagus or accumulation of secretions in the tracheobronchial tree. In some patients, the "reflex apnea" was initiated by stimulation of the area of tracheal compression during tracheobronchoscopy. Reflex apnea was considered an indication for surgical relief of tracheal compression to interrupt some reflex arch [16].

During the 1970s, attention was drawn to the concept that in infants with repaired esophageal

atresia, tracheomalacia, that is, a weak tracheal wall, may be a major factor responsible for the collapse of the thoracic trachea [25–28]. The temporal correlation with feeding was explained by considering that the dilated upper esophagus, filled during swallowing or after a gastroesophageal reflux, increases the compression of the malacic trachea against the anomalous vessel anteriorly [27, 32]. A further step in the understanding of ALTE pathogenesis in infants with esophageal atresia was the finding that transcutaneous monitoring of PO2 during feeding in infants with a history of ALTE showed a significant hypoxemia [32]. This finding supported the previous concept that not a vagal reflex but severe hypoxemia due to tracheal obstruction can be responsible for ALTE [27]. In this view, tracheopexy serves to relieve the tracheal obstruction.

Southall et al. have studied the mechanism responsible of ALTE in a large series of infants with recurrent cyanotic attacks, including three infants with repaired esophageal atresia [12, 31, 34, 36]. All three infants with repaired esophageal atresia had recurrent episodes of ALTE without evidence of associated obstructed inspiratory effort. One patient previously underwent an aortopexy and a fundoplication; another underwent an aortopexy, and the last one underwent a tracheostomy for acute airway obstruction considered to be the cause of ALTE. In these three patients, surgery reduced or had no impact on the frequency and severity of ALTE without respiratory distress [34, 36]. In one of these patients, the first event detected before ALTE by the parents and hospital staff was an audible grunting, followed by the onset of cyanosis within 5–10 s. By 20 s the patient was deeply cyanosed and seemed unconscious [34]. As previously pointed out [4], Southall et al. concluded that the rapid onset of cyanosis cannot be explained by a simple upper airway obstruction. Actually in infants in whom an airway obstruction was imposed by maternal smothering, arterial hypoxemia sufficient to produce cerebral anoxia was delayed for 60–72 s [35]. In addition, an upper airway obstruction was not considered to be the cause of ALTE because ALTE continued despite nasotracheal intubation in one case or tracheostomy in another case [34, 36]. In their view, the rapid desaturation was due to a sudden right-to-left intrapulmonary shunt, "sudden atelectasis braking syndrome," brought about by an exaggerated expiratory effort, by "prolonged expiratory apnea," and/or by low lung volume brought about by abnormal surfactant [31]. Support for the concept of a right-to-left shunt is due to a sudden lung collapse that comes from the autopsy findings of an infant with esophageal atresia, who was found dead in the incubator on the third day after primary anastomosis: postmortem examination showed only the presence of widespread pulmonary atelectasis [17].

Vagal reflexes from lung mecanoreceptors play an important role in the organization of active expiration [9]. This is a breathing strategy adopted by infants with a low lung volume. An active interruption of expiratory flow by glottis adduction associated with a positive expiratory pressure (equivalent of Valsalva's maneuver) serves to maintain patency of alveoli by forcing gas retrogradely into the peripheral airway; grunting is the clinical manifestation of an active expiration. An abnormal response to this protective lung reflex may provide an explanation for the "prolonged expiratory apnea" and for the respiratory arrest in expiration [9]. Accordingly, Southall postulated that the surgical repair of esophageal atresia may damage the autonomic innervation of the lung with the result that abnormal lung reflexes may be responsible of the prolonged expiratory apnea. Iatrogenic damage of autonomic innervation of the lung may also interfere with an abnormal synthesis of lung surfactant which may result in a low lung volume [12]. The main criticism to this concept is that in infants with esophageal atresia, ALTE may occur even before the surgical repair [37]. In addition, ALTE is a manifestation of a more general dysautonomia affecting multiple vagal target sites [37, 48].

During the last 40 years, our group has contributed to the understanding of the pathogenesis of ALTE associated with respiratory distress [7, 14, 37, 41, 42, 44, 45, 48]. In 1977, the senior author speculated that in infants with esophageal atresia, the pathogenesis of ALTE may be similar

to that of life-threatening apnea in infants with choanal atresia, or Pierre Robin syndrome, or hypertrophied adenoids and sleep apnea [7]. In this view, the life-threatening apnea was sustained by an obstruction of the upper airway caused by a backward aspiration of the tongue. This functional obstruction of the pharynx was originally described by Pierre Robin in infants with micrognathia and called "glossoptosis" [1]. In Pierre Robin view, the backward displacement of the tongue was a mechanical consequence of a short mandible. Our physiological studies supported the concept that glossoptosis was the consequence of strong aspirating forces brought about by strong inspiratory efforts [7].

Subsequent clinical and physiological studies suggested that even mild inspiratory efforts, brought about by simple rhinitis if not counterbalanced by an appropriate reflex activity of upper airway dilating muscles, may cause an inspiratory collapse of the laryngeal and/or pharyngeal airways [14]. Therefore, in infants with different types of upper airway anatomical or inflammatory narrowing, the important pathogenetic factor for upper airway inspiratory collapse to occur appears to be a disorder of the autonomic control of the upper airway dilating muscles.

The concept of a developmental delay of autonomic control of respiration is supported by the findings of our studies on breathing patterns in some infants with esophageal atresia associated with ALTE and inspiratory dyspnea [37, 41]. The mild inspiratory load imposed by tilting the infant from the lateral to the supine position was not followed by an appropriate reflex activity of upper airway dilating muscles because it resulted in a sharp reduction of the inspiratory airflow despite a marked increase of inspiratory effort (Fig. 46.1). This obstructive hypopnea was accompanied by an audible inspiratory stridor [37].

Recurrent episodes of functional upper airway obstruction usually cause an alveolar hypoventilation characterized by hypoxemia and hypercapnia. However, infants with esophageal atresia [44], like those with choanal atresia or congenital micrognathia [14], often show a blood gas derangement characterized by hypoxema without hypercapnia. The most frequent chest films findings are the presence of some atelectatic areas of the lung associated with other hyperinflated areas of the lung [14, 44]. Normal perfusion of hypoventilated areas of the lung may explain the hypoxemia. The hyperventilation of some other areas of the lung may explain the normocapnia.

In our series of patients with esophageal atresia or choanal atresia, or congenital micrognathia, the requirement of oxygen concentration in the inspired air to maintain an oxygen blood concentration between 60 and 80 mmHg was often surprisingly high considered the limited extent of chest films

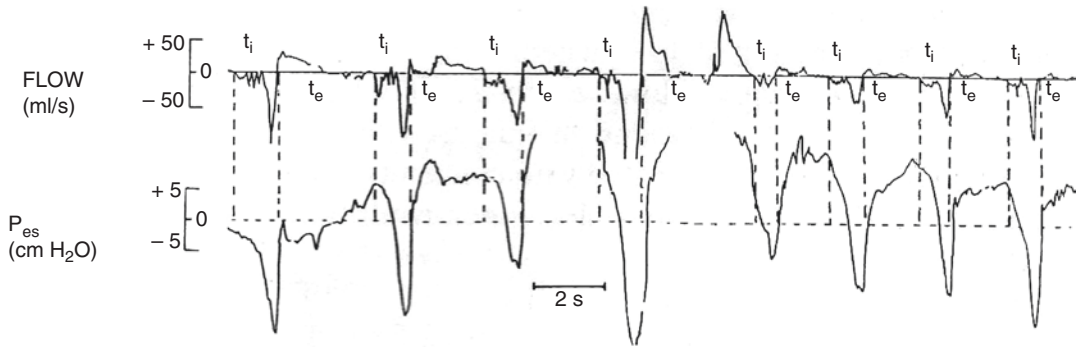

Fig. 46.1 Infant with esophageal atresia and distal tracheoesophageal fistula. The postural respiratory loading imposed by tilting the infant from the lateral to the supine position resulted in a retarded and reduced inspiratory flow despite increased inspiratory efforts (obstructive hypopnea). Note: the obstructive hypopnea is followed by prolongation of the expiratory time and interruption of the expiratory flow associated with positive expiratory pressure. Ti and Te: inspiratory and expiratory time, respectively

opacities. Consequently, patients breathing at high oxygen concentration in the inspired air develop a considerable alveolar-arterial oxygen difference (Fig. 46.2). The best explanation of these findings is that the upper airway functional obstruction associated with variable anatomical airway narrowing causes the development of a lower airway instability due to ventilation/perfusion inequalities and an intrapulmonary right-to-left shunt. Actually, oxygen, compared with other gases, is more rapidly absorbed from the alveolus. Therefore, alveolar hyperoxia due to an increased delivery of oxygen converts into atelectasis those segments of the lung with a low ventilation to perfusion ratio where the absorption exceeds the rate of delivery of oxygen [14, 44].

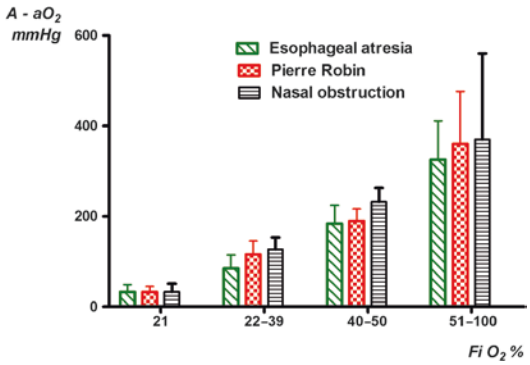

Fig. 46.2 In infants with different anatomical causes of upper airway obstruction, greater pressure of inspired oxygen (FiO2) results in large alveolar-arterial oxygen difference (A-aO2), suggesting intrapulmonary right-to-left shunt

Accordingly, in two infants with repaired esophageal atresia, who presented with recurrent ALTEs percutaneous arterial PO2 and PCO2 measurement while breathing 100 % oxygen administered in a plastic hood showed only moderate increase in PO2 and normal PCO2 (Fig. 46.3). The two infants showed no blood gas derangement and, on chest films, no lung opacities. These findings are consistent with the development of a considerable right-to-left shunt caused by absorption collapse of some hypoventilated areas of the lung. The breathing oxygen test returned to normal shortly after glossopexy, a surgical procedure which serves to stabilize the upper airways [42, 45]. These findings allow us to exclude the presence of an extra-pulmonary right-to-left shunt and suggest that the lower airway instability was sustained by recurrent episodes of obstruction in the upper airway [42].

In our series of infants with different types of upper airway anatomical narrowing, the correlation between upper and lower airway instabilities was also indicated by our studies of the breathing patterns, showing that obstructive apneas (Fig. 46.1) as well as central apnea (Fig. 46.4) were immediately followed by an active expiration, which is the breathing strategy adopted in presence of a lower airway instability due to a

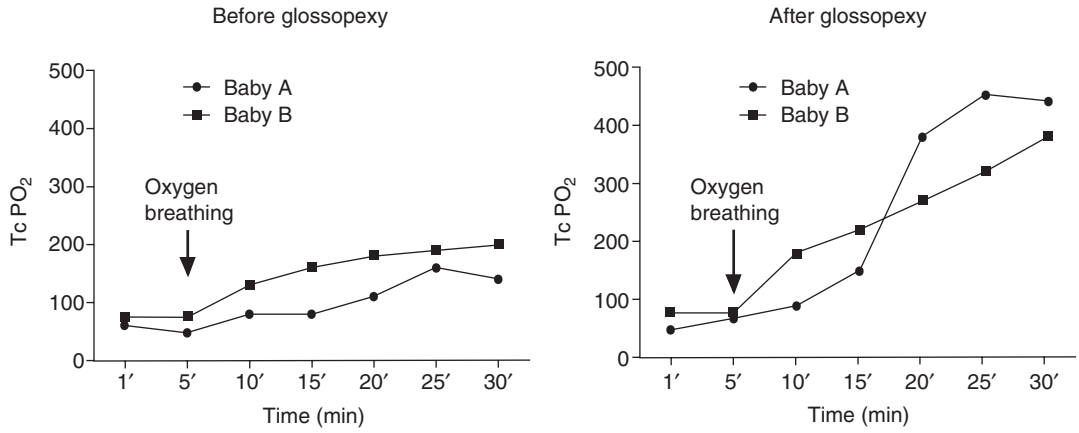

Fig. 46.3 Breathing oxygen test in two infants with repaired esophageal atresia. Note: development of a relevant right-to-left shunt (15–20 %) before glossopexy; normal breathing oxygen test shortly after glossopexy

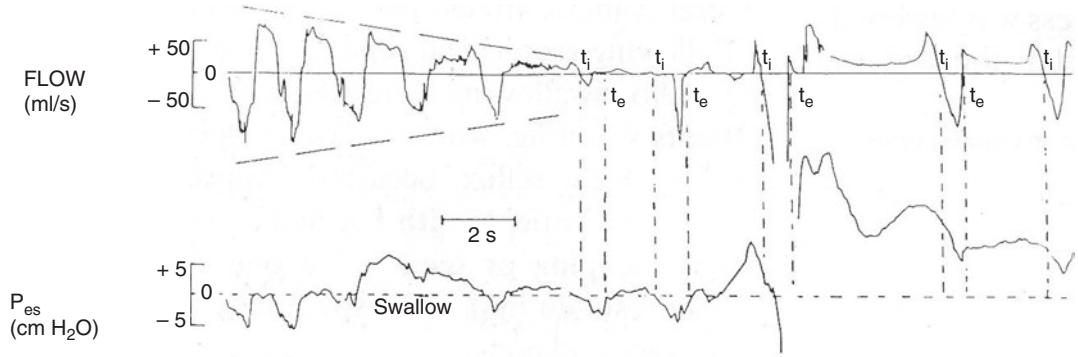

Fig. 46.4 Infant with esophageal atresia and distal tracheoesophageal fistula. Swallowing is associated with a parallel reduction of inspiratory flow and inspiratory efforts (central hypopnea). Note: central hypopnea is followed by grunting expiration. Ti and Te: inspiratory and expiratory time, respectively

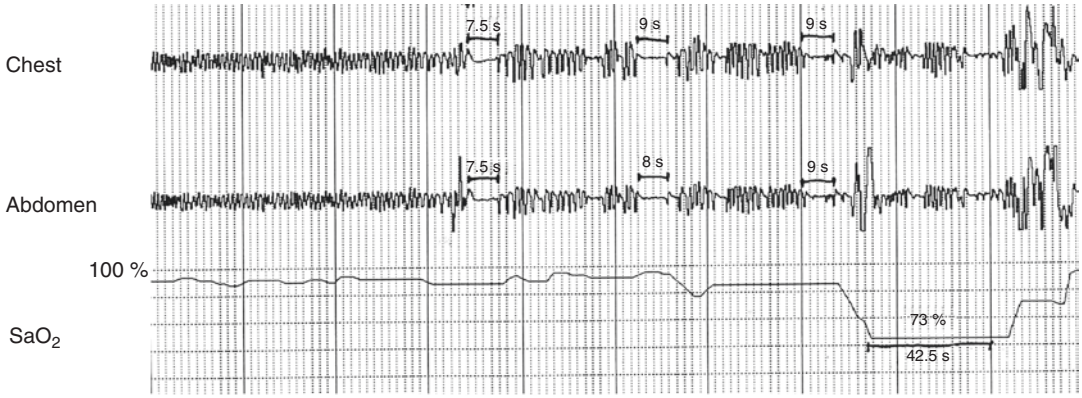

Fig. 46.5 Infant with esophageal atresia with feeding gastrostomy and continuous suction of the blind upper esophageal pouch. Accumulation of saliva in the upper pouch is followed by periodic breathing. Note: repetitive apneic pauses of similar short duration are followed by a sudden and severe desaturation suggesting a right-to-left shunt, due to developing microatelectasis

low lung volume [37, 45] (Fig. 46.1). These findings suggest that not only obstructive but also central apneas may be responsible of lower airway instability. Repetitive central apneas hypopneas may cause a progressive fall in lung volume resulting in a sudden and severe desaturation probably due to the development of alveolar collapse and right-to left shunt [48] (Fig. 46.5).

The respiratory status we found in infants with an inspiratory obstruction associated with various congenital anomalies of upper airways is quite similar to the respiratory status found in infants with inspiratory stridor caused by inflammatory upper airway obstruction. In infants with epiglottitis, radiologic and gas exchange abnormalities, similar to those we found in our series of patients with various upper airway congenital anomalies, were considered to be the consequence of an increase in lung water [8, 13, 24]. During phases of moderate inspiratory respiratory distress, interstitial flooding causes peribronchial edema, small airway closure, and military atelectasis [13, 24]. This segmental collapse of dependent zones of the lung is not detected on conventional chest films [10] and may be responsible for the modest ventilation/perfusion mismatch with hypoxemia. Arterial PCO2 may be normal because of compensatory hyperventilation of uninvolved pulmonary segments. This pathophysiological mechanism may

well explain the hypoxemia without hypercapnia and with clear chest films.

According to Costigan et al. [13], during phases of more severe inspiratory distress, a widespread alveolar flooding causes major atelectasis, which is visible on chest films. Accordingly, in our series of patients, lung opacities frequently cleared up on subsequent films, indicating lung collapse more than consolidation [14, 37, 44]. In addition, the "butterfly pattern" frequently found on chest films is consistent with the diagnosis of pulmonary edema [44]. Actually, postmortem examination of the child who died during a cyanotic episodes following food bolus impaction in the esophagus showed only pulmonary edema [34].

To investigate whether feeding, gastroesophageal reflux, tracheomalacia, and upper airway instability are independent or interrelated factors, we studied the clinical manifestations of patients with esophageal atresia treated with a cervical esophagostomy and/or a gastrostomy [48]. The presence of a gastrostomy and a blind lower esophageal stump rules out the putative pathogenetic role of gastroesophageal reflux as well as the role of feeding. The cervical esophagostomy rules out the putative pathogenetic role of tracheal stenosis. In our study, eight of nine patients with a feeding gastrostomy and with a continuous suction of the blind upper esophageal pouch presented with ALTEs either associated or not with signs of airways obstruction. Subsequently, for the presence of respiratory problems, five of the nine patients underwent an esophagostomy. In addition the other six patients underwent an esophagostomy as a primary procedure. Of the 11 patients with a cervical esophagostomy and a feeding gastrostomy, 5 presented signs of airways obstruction without ALTE and 6 ALTE without signs of airways obstruction. Trigger factors of respiratory distress and central and/or obstructive ALTE were upper respiratory tract infections, swallowing, crying, anesthesia, sedation, and sleeping. These findings strongly suggest that feeding, gastroesophageal reflux, and tracheomalacia may trigger ALTE but are not essential for ALTE to occur. In our opinion, the principal pathogenetic factor seems to be a development delay of the respiratory control. Feeding, gastroesophageal reflux, and tracheomalacia, like many other trigger factors, probably offer evidence of an underlying dysautonomic problem [48].

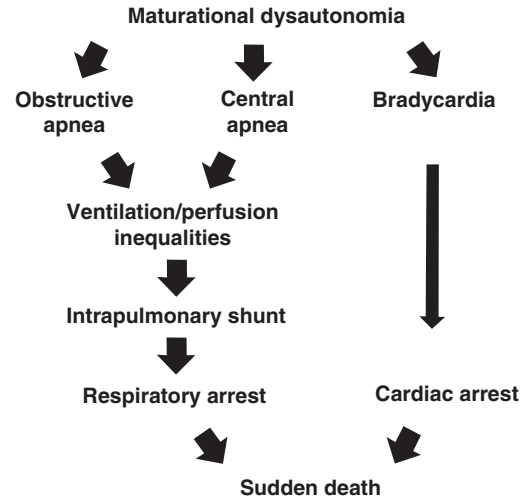

Fig. 46.6 Putative respiratory and cardiac pathways for apparent life-threatening event and sudden death in infants with esophageal atresia

In few reported cases, a different pathogenetic mechanism of ALTE has been documented, that is, a primary reflex bradycardia followed by cardiac arrest [21, 23, 30, 37]. The vagus nerve has a depressant action on the sinus pacemaker; hypersensitivity of this inhibition reflex may cause a cardiac arrest; the consequent circulatory failure causes cerebral anoxia which may progress to ALTE and even to sudden death [21]. Probably, the condition of cardiac arrest due to an overactive vagal reflex is largely overlooked [23, 30]. Actually, the diagnosis can be made with certainty only in infants on continuous cardiac activity monitoring.

On the basis of available evidence, we suggest that in infants with EA, the pathogenesis of ALTE and sudden death may be considered as a cascade reaction (Fig. 46.6). Babies born with esophageal atresia may present a development delay of the regulation of respiratory and cardiac functions. The dysfunction of respiratory control causes obstructive and/or central apneas/hypopneas that in turn cause ventilation/perfusion inequalities, intrapulmonary shunt, severe hypoxemia, and

eventually a respiratory arrest. The dysfunction of cardiac rhythm may cause bradycardia and eventually cardiac arrest. Both respiratory and cardiac arrests may progress to sudden death.

Clinical Manifestations

In infants with esophageal atresia, the prevalence of ALTE is difficult to determine because the differences between respiratory distress and ALTE or between cyanotic attacks and ALTE are most often not specified. In addition the prevalence of ALTE not treated by surgery is usually not reported, and the choice to treat ALTE surgically is subjective. In a series of 148 patients with esophageal atresia treated at The Hospital for Sick Children, Great Ormond Street, London [33], 21 infants developed "significant gastroesophageal reflux sufficient to cause life-threatening episodes" (18 %), and 19 infants presented "tracheomalacia severe enough to cause serious respiratory embarrassment" (16 %). In our own series of cases with esophageal atresia, we found a prevalence of 30 %, life-threatening episodes requiring resuscitation, including ALTEs that resolved spontaneously [37]. Similarly, in a series of 371 patients treated at the Pediatric Surgical Center of Amsterdam [46], 87 patients presented recurrent respiratory problems (32 %). These data, taken together, suggest that in infants with esophageal atresia, ALTE is a frequent complication.

Three different clinical forms of ALTE have been described. The most frequent reported clinical form, originally described by Mercer, is characterized by recurrent episodes of upper airway obstruction which precede ALTE. We described in the chapter on choanal atresia the clinical manifestations of the respiratory distress. Often the inspiratory dyspnea is associated with signs of expiratory dyspnea, which may simulate an asthmatic attack [41]. Characteristically, ALTE is observed after the first few months of life. The reason for this late presentation is considered obscure [32]. Probably, these clinical findings support the concept that recurrent episodes of upper airway obstruction causes a pulmonary status which subsequently predispose to ALTE [44].

The other clinical form of ALTE is characterized by a respiratory arrest not associated with signs of inspiratory efforts (central apnea). This form was originally described by Allen et al. [20]. Subsequently, Fearon and Shortreed called "reflex apnea" an ALTE induced under light general anesthesia when a bronchoscope was passed through the compressed area of the trachea [16]. In an infant with repaired esophageal atresia, this form of ALTE has been reproduced by inflating a latex balloon within the upper third of the esophagus [36]. In an infant with long-gap esophageal atresia, before the continuity of alimentary tract was established, we observed that the accumulation of saliva in the upper pouch caused periodic breathing associated with significant desaturation (Fig. 46.5) [48]. ALTE induced by a bolus of food impacted within the upper esophagus may progress to sudden death [34, 37].

ALTE without inspiratory efforts most often occurs after crying rather than swallowing [37]. In our experience, this form of ALTE is most often triggered by upper respiratory tract infections; other favoring factors are sleeping, sedatives, and anesthesia [48]. Also this form of ALTE has a late presentation and is preceded by recurrent episodes of apnea without inspiratory efforts [37, 48]. Central apnea, especially if occurs during sleep, may easily be overlooked even if associated with desaturation.

The third clinical form is characterized by an ALTE sustained by a reflex bradycardic arrest. In 1959, Bauer et al. described in an infant, who had a thoracic transposition of the stomach to bridge the gap of an esophageal atresia without tracheoesophageal atresia, an episode of bradycardia with sinoatrial block and appearance of a slow AV rhythm. This infant died in the 34th postoperative day during one of these cyanotic episodes. At autopsy, the vagus nerve was found to be compressed in the upper chest by a dilated stomach. It was thought that the severe bradycardia was brought about by stimulation of vagus nerve due to gastric distension [21].

Very few cases with this form of ALTE have since been described [23, 30, 37]. These patients

may become symptomatic at "different stages of development" but usually are diagnosed during first admission for a direct stimulation of the thoracic vagus nerve [21, 30, 37]. However, an ominous fetal bradycardia may be detected during the last weeks of gestation or during delivery, requiring an emergency caesarean section [37]. One patient with repaired esophageal atresia presented a reflex bradycardic ALTE at the age of 2 years, when she was eating some solid food [23]. One of our patients presented a reversible bradycardic cardiac arrest probably sustained by a mechanical manipulation of the nerve vagus during primary esophageal repair. Subsequently, this patient presented two new cardiac arrests requiring a cardiac message during esophageal dilatation under general anesthesia given through a tracheal tube [37]. Another of our patients with esophageal atresia had a bradycardic arrest during esophageal dilatation under general anesthesia. In addition, this patient at the age of 4 years presented an episode of ALTE triggered by a mild frightening injury [48].

In infants with esophageal atresia, ALTEs are very often associated with other dysautonomic features including oropharyngeal dysphagia, regurgitation, vomiting, hyperhidrosis, hyperthermia, and bradycardia [37, 48]. In addition, nearly all patients present the characteristic seal-like bark cough due to the associated tracheomalacia. Main complications of infants with glossoptosis syndrome include failure to thrive, cor pulmonale, and asphyxic brain damage [14].

Evaluation and Surgical Management of Underlying Disorders

In infants with esophageal atresia, the underlying disorders currently considered to be surgically correctable causes of ALTE include gastroesophageal reflux, tracheal compression/tracheomalacia, and upper airway instability.

Gastroesophageal reflux is usually diagnosed with radiological investigations and esophageal pH probe monitoring. In infants with repaired esophageal atresia, the occurrence of gastroesophageal reflux is rather frequent. In a series of 120 patients, routine pH measurement showed gastroesophageal reflux in 53 patients (41 %); failure of medical therapy was the indication for surgical antireflux procedure in 41 (77 %) patients [46]. The other characteristic of gastroesophageal reflux in infants with repaired esophageal atresia is that only half of the patients improved after fundoplication mainly for the presence of respiratory symptoms, or emesis, or failure to thrive [40, 43]. There are a few reports regarding specifically the results of surgical treatment of gastroesophageal reflux to prevent recurrent ALTE; available data suggest that fundoplication appears to be an effective method for preventing recurrent ALTE [28, 29].

Tracheomalacia can be diagnosed on clinical grounds from the presence of the typical brassy cough. However, the severity of tracheomalacia must be assessed by means of a bronchoscopy in a patient breathing spontaneously. The well-accepted treatment of tracheomalacia is aortopexy [19, 26, 27]. Splinting of the trachea may be an alternative but does not reverse ALTE. In infants with esophageal atresia, the results of tracheopexy for ALTE are usually considered good [38, 39, 46]; however, in a minority of cases, ALTE may persist after aortopexy [36, 38, 47].

If gastroesophageal reflux and tracheomalacia coexist, the decision to proceed with tracheopexy or fundoplication is usually based on the impression of each surgeon. Before taking the decision, it is of paramount importance to exclude the presence of a concomitant recurrent tracheoesophageal fistula. To evaluate the results obtained when tracheomalacia and gastroesophageal reflux coexist, Nasr et al. reviewed the experience at the Hospital for Sick Children of Toronto. Of 288 patients with esophageal atresia, 22 developed a severe respiratory distress which was related to tracheomalacia or gastroesophageal reflux. Severe respiratory distress included pneumonia (two cases), blue spells (ten cases), and ALTE (ten cases). Thirteen infants had an aortopexy or a tracheal splint. Of these, seven patients (including three with ALTE) improved, and six (46 %) required subsequent fundoplication for ongoing respiratory problems. Nine infants had an initial

fundoplication. Of these, six patients (including two with ALTE) improved, and three required an aortopexy or a tracheal splint for ongoing respiratory problems. Overall, nine patients (including five patients with ALTE) improved only after the second procedure [47].

The diagnosis of upper airway instability may be made on a clinical ground. The presence of inspiratory efforts with poor or absent air entry, usually associated with a clear chest X-ray, is a clinical manifestation of partial or total upper airway obstruction (obstructive apnea or hypopnea). On examination, glossoptosis and inspiratory retractions of the soft part of the neck (especially suprasternal notch) are usually observed. The inspiratory efforts are very often associated with inspiratory stridor or noisy inspiration. The additional clinical signs of functional inspiratory obstruction include open-mouth breathing and head extension (opisthotonus). The severe phases of inspiratory dyspnea are associated with signs of expiratory obstruction including grunting/wheezing and ballooning on expiration of cheeks and soft part of the neck. In infants with esophageal atresia, the expiratory dyspnea is conventionally attributed to tracheomalacia. However, an active expiration, that is, adduction of the vocal cords associated with a positive expiratory pressure, may contribute to the clinical manifestations of a functional expiratory obstruction (equivalent of Valsalva's maneuver). The sign of an active expiration is prolonged expiration associated with grunting. Grunting may simulate a wheezing but may be easily differentiated because grunting is loudest over the neck, whereas wheezing is loudest over the thorax. In infants with ALTE, grunting should be considered a clinical manifestation of lower airway instability until otherwise proved. In some infants with esophageal atresia, the recurrent episode diagnosed as "bronchiolitis" or as "asthmatic attacks" [28] may be sustained by a not recognized active expiration [42].

To document the frequency and the severity of central and obstructive apneas especially during sleep, polysomnography can be a useful investigation. The site of functional upper airway obstruction can be documented with the use of cineradiography. Endoscopic examination of the upper airway during spontaneous breathing may document the diagnosis of pharyngomalacia (glossoptotic pharyngeal obstruction) or laryngomalacia. As the presence of a lower airway instability in our opinion should prompt a treatment of the associated upper airway instability, we have found useful to document the presence of areas of ventilation/perfusion inequalities with the aid of 100 % O_2 breathing test. Having the patient to breathe oxygen for up 20–30 min, a sample of arterial blood is obtained for PaO_2 and hemoglobin concentration determinations. The ratio of right-to-left shunt flow to total systemic blood flow may be calculated.

The presence of an elevated right-to-left shunt allows one to identify those patients who are susceptible to ALTE for the development of lung collapse (Fig. 46.3).

In infants with Pierre Robin syndrome, ALTEs have been successfully treated by lip-tongue adhesions (glossopexy) [5, 6]. Similar good results have been obtained by glossopexy in infants with esophageal atresia and ALTE [42, 45]. These good results, as those reported after fundoplication or after aortopexy, may be only temporary and not casually related with surgery, because ALTEs tend to disappear spontaneously. However, the rapid improvement of clinical manifestations related to upper and lower airway instabilities and the rapid improvement of blood gas derangements (Fig. 46.3) strongly suggest that glossopexy stabilizes the upper and lower airways. For those infants who do not solve the problem of ALTE with a glossopexy, mandibular distraction may avoid glossoptotic pharyngeal obstruction. If necessary, tracheostomy will prevent episodes of recurrent upper airway obstruction. As in infancy, tracheostomy has a relevant morbidity, a less invasive alternative can be aortopexy or fundoplication performed with the rationale to avoid the additional respiratory load imposed by tracheomalacia or by gastroesophageal reflux [48].

Acknowledgments We wish to thank Dr. S. Frediani for his help and comments in the preparation of this chapter.

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New Insights and Applications in the Treatment of Nerve Injuries

47

Alison K. Snyder-Warwick, Andrew Yee, and Susan E. Mackinnon

Introduction

Peripheral nerve injuries can have devastating functional consequences. Particularly in the pediatric population, nerve injuries may have negative implications on growth, mobility, and quality of life. While prevention is the most effective treatment for injury, nerve pathology pervades all age groups and all subspecialties. Peripheral nerve disorders may result from mechanical, infectious, iatrogenic, immunologic, oncologic, and traumatic etiologies. Cosmesis has psychosocial importance, but restoration of function is paramount in planning nerve reconstructions. Historically, treatment of peripheral nerve injuries had limited application and suboptimal results. While the advancement of microsurgical technique as well as our understanding of nerve injury and regeneration has led to improved technical ability to repair nerve pathology, the slow rate of neuroregeneration has limited the results of treatment of proximal nerve injury. The last decades of work have helped shape the novel concept of treating proximal peripheral nerve injuries with a distal reconstruction via nerve transfers. This chapter reviews special considerations specific to nerve injury in the pediatric population, the mechanisms of neuroregeneration, obstacles in muscular reinnervation after injury, and modern approaches to the treatment of peripheral nerve injuries in children.

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Nerve Injuries in Children

Pediatric patients possess extraordinary healing potential. Peripheral nerve surgeons have long held the belief that identical peripheral nerve injuries have much better prognosis in children compared to adults [34], and scientific data are now available to support this clinical observation. After crush injury, immature rats demonstrate less functional impairment at 2 weeks when compared to identically treated adults [4]. Immature nerves regenerate faster [62], with some reports describing rates of up to five times the rate of adult peripheral nerve regeneration [76]. Neonatal experimental models have also demonstrated greater maintenance of somatotopy and improved target specificity of neuroregeneration compared to adults [1]. In addition, the distances required for nerves to regenerate in order to achieve target reinnervation are smaller compared to those in adults. All of these factors result in reduced time to reinnervation, and the importance of this timing will be discussed in relation to the muscular motor end plates in a later section. Rapid reinnervation of target

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muscle results in improved functional outcomes. Children also demonstrate greater cortical and neuronal plasticity [47, 90] and are therefore better able to adapt not only to altered patterns of peripheral innervation but also retraining that may be required as a result of reconstructive techniques.

Despite these advantages, treatment of peripheral nerve injuries in children also presents challenges. The physical examination and diagnosis of nerve injuries in children can be difficult if the patient is young and unable to follow commands. Examination is based largely on observation of posture and abdominal and thoracic symmetry with breathing (in the case of the phrenic nerve) [11, 94], spontaneous activity, and reward-based prompting for the child to reach for objects, both with and without the assistance of gravity. Depending on the diagnosis, nerve injury may also be quite painful, and care should be taken to control pain and minimize undue stress as much as possible. Patients should be examined in a comfortable setting, such as a parent's lap or while playing. Pain control should not be ignored. Because of communication barriers due to developmental stage, the treating physician should maintain a high index of suspicion for injury and discomfort. In addition, rehabilitation presents additional challenges for the child that cannot yet follow instructions. Therapy can be based on motivators, such as visually stimulating toys, and is a team endeavor involving the physician, therapist, and caregiver.

Peripheral Nerve Fiber and Fascicular Anatomy

Knowledge of normal peripheral nerve anatomy and physiology is an imperative prerequisite to managing peripheral nerve injuries. Peripheral nerves are comprised of mature axons that are encapsulated by Schwann cells and are either myelinated or unmyelinated (Fig. 47.1). Unmyelinated fibers are composed of several axons, surrounded by a Schwann cell and its dual layer basement membrane. The axons of myelinated nerve fibers are also surrounded by a Schwann cell, which instead forms a multi-laminated myelin sheath. Individual myelinated nerve fibers and groups

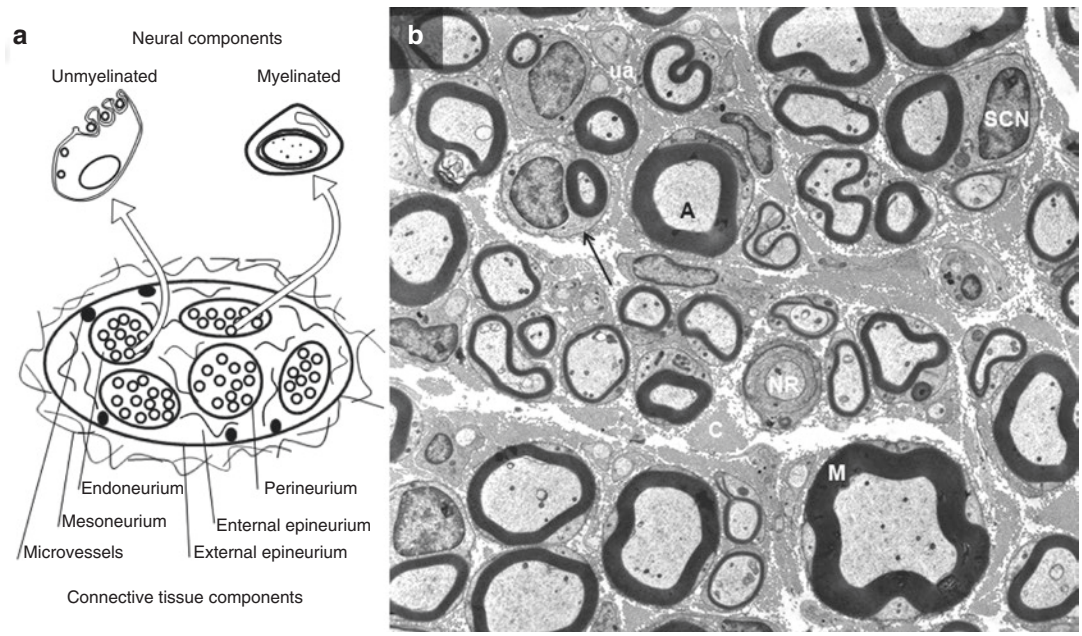

Fig. 47.1 Normal peripheral nerve morphology. (**a**) The peripheral nerve is composed of neural and connective tissue components. The nerve fiber is either unmyelinated or myelinated. (**b**) An electron microscopy image of a population of myelinated and unmyelinated nerve fibers. *M* myelin, *A* axon, *SCN* Schwann cell nucleus, *arrow* double basement membrane, *C* endoneurial collagen, *ua* unmyelinated axon, *NR* node of Ranvier (Uranyl acetate, 4750× magnification)

of unmyelinated fibers are surrounded by a Schwann cell-derived double membrane of basal lamella.

Surrounding the individual myelinated nerve fibers and groups of unmyelinated nerve fibers are thin collagen fibers known as the endoneurium. These myelinated and unmyelinated nerve fibers collect together to form a fascicle, and fascicles are bound by a discrete connective tissue sheath called perineurium. The connective tissue that surrounds the individual fascicles is termed the internal (intrafascicular) epineurium, while the connective tissue that surrounds the entire nerve is termed the external (extrafascicular) epineurium. A loose areolar tissue that surrounds the nerve and extends from the epineurium to the surrounding tissue is known as the mesoneurium. The mesoneurium is continuous with the perineurium and is critical in longitudinal gliding of the nerve.

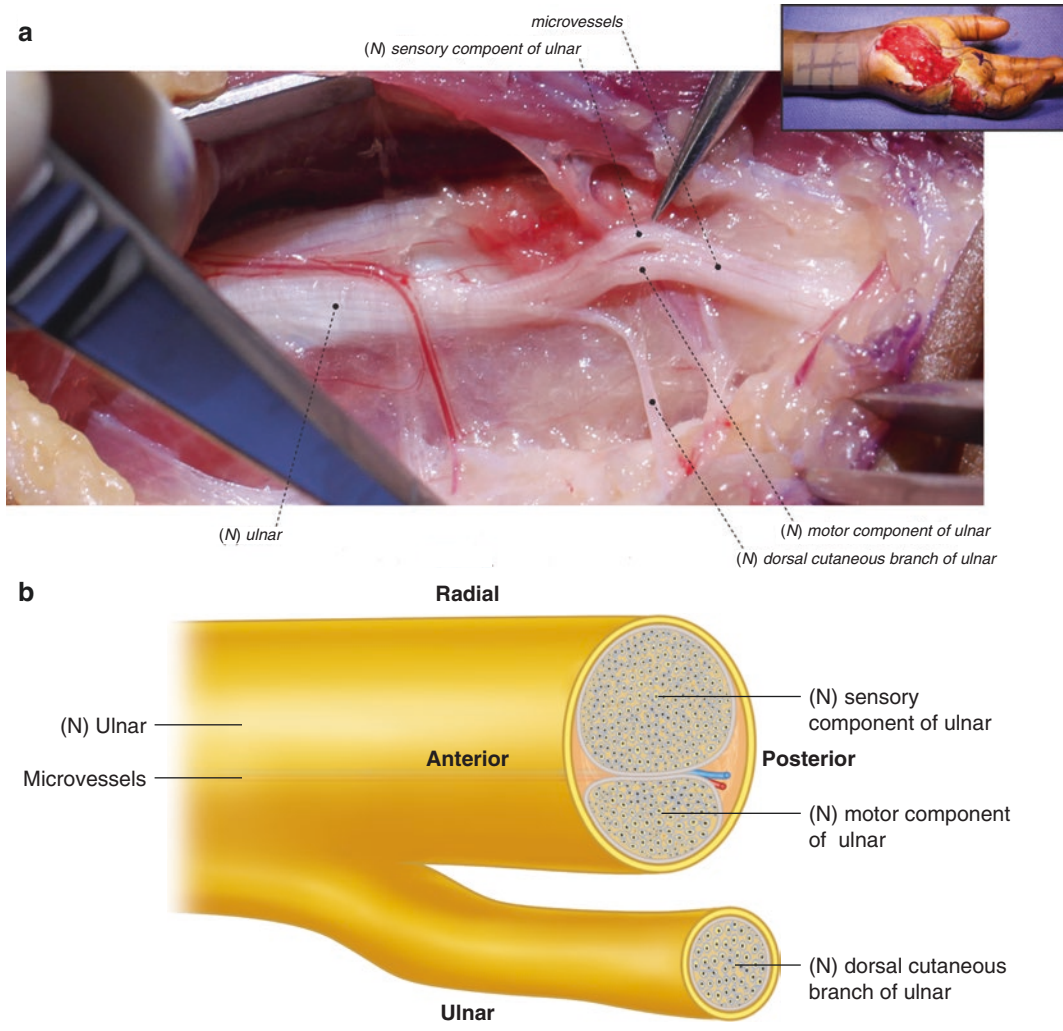

Fig. 47.2 Internal topography of the ulnar nerve in the forearm (**a**). Knowledge of internal topography of peripheral nerves is critical for nerve repair to optimize the specificity of modality- and function-matched reinnervation. As an example (**b**), the ulnar nerve in the forearm has three components. The sensory component is found on the radial half of the ulnar nerve. The motor component is found adjacent and ulnar to the sensory component. This component becomes the deep motor branch distally. The dorsal cutaneous branch is found ulnar to the motor component and branches distally to innervate the ulnar dorsal cutaneous aspect of the hand. *N* nerve

There are three basic types of fascicular nerve patterns: monofascicular with just one large fascicle, oligofascicular consisting of a few fascicles, and polyfascicular consisting of many fascicles of varying sizes. In relation to the extremities, monofascicular patterns are found in the proximal extremity with each fascicle consisting of a mixture of motor and sensory fibers. There is considerable plexus formation among fascicles in the proximal extremity. This pattern decreases as the nerve travels distally becoming polyfascicular in the distal extremity and further differentiates into motor and sensory components [39, 95].

Knowledge of the internal topography of peripheral nerves directs the proper alignment of fascicles during nerve repair to optimize the specificity of modality- and function-matched reinnervation (Fig. 47.2). Mismatched modality and/or function in nerve repairs dramatically downgrades the outcome following nerve reconstruction. This topographical knowledge has resulted predominantly from intraoperative electrical stimulation of nerves to identify specific motor and sensory components [14]. Electrical stimulation has been a viable tool not only in identifying and confirming the internal topography of a nerve but also to confirm function or loss of function after nerve injury.

Mechanism of Neurodegeneration and Neuroregeneration

The neuronal response to injury depends on a number of factors which include mechanism of injury, patient age, and the injury proximity to the cell body. The mechanism that regulates the cell body response, axonal projection, and terminal synaptogenesis of a single neuron after injury is thought to be regulated locally. As a result, compromise to a proximal compartment may not spell demise to the distal compartment. This "compartmental view of neurodegeneration," as termed by Gillingwater and Ribchester [24], is used to describe the multilevel response to peripheral nerve injury. The most devastating level of injury to a motor neuron is proximally either by avulsion, direct lesion, or other injuries [46, 48], which results in the death of the individual neuron. Proximal neuronal injury is devastating in neonates with demise of up to 60–70 % of involved motor neurons reported in the murine model [3, 55, 86, 87]. Currently, the reconstruction of choice for proximal nerve injuries is distal nerve transfer.

Wallerian degeneration is a process that occurs at the distal segment of an injured nerve fiber. This process is described as Schwann cells, fibroblasts, myocytes, and injured axons expressing a host of neurotrophic factors in response to injury as the degrading neural elements are phagocytosed [2, 24, 25, 28, 35, 36, 53, 75, 79]. Proximal axonal injuries and avulsions lead to injury-induced cell death with loss of the cell body and its projections. The cell body is maintained following a distal axonal injury with preservation of its regenerative potential [17]. The distal axonal segment to the injury undergoes Wallerian degeneration. In situations of prolonged denervation of 6 months or later, Schwann cells in the distal nerve segment provide less trophic support and may even undergo apoptosis [73]. This may explain impaired nerve regeneration following delayed nerve injury repair.

Recovery following peripheral nerve injury is influenced by the relative distance of the injury to the cell body and is characterized by the specific changes both proximal and distal to the site of injury [22]. Following injury, the proximal axons retract a variable distance and undergo a brief dormant phase, during which molecular signaling cascades are initiated and neurotrophic factors are shuttled, before the formation of a regenerating unit [26]. The regenerating unit elongates with a single parent axon and sprouts multiple daughter axons, having an appearance of a hydra [20]. In myelinated nerve fibers, axons sprout from the gap between myelin sheaths, also known as nodes of Ranvier, and progress to their motor or sensory targets. Nerve fibers regenerate at a rate of ~1 mm daily or ~1 in. per month. Schwann cells have a pro-regenerative phenotype that is critical in remyelinating and guiding axons to their appropriate targets along residual endoneurial tubes known as bands of Bungner [29, 33, 40, 41, 51, 54, 80]. Once an axon projecting from

the regenerating unit attaches to its target and forms a functional synapse, the remaining daughter axons are "pruned back," creating a one-to-one relationship between the neuron and end organ.

Classification of Nerve Injury

Classification of peripheral nerve injuries and knowledge of the degree of nerve injury are critical both for prognosis and surgical planning when determining potential for nerve reconstruction [71]. The three categories of nerve injury (neurapraxia, axonotmesis, and neurotmesis) were first described by Seddon in 1943 and were later expanded in 1951 by Sunderland using five degrees of nerve injury [31, 72]. Mackinnon popularized the sixth degree of injury to describe mixed-degree injuries, which encompass two or more injury patterns at the same level of disruption (Fig. 47.3) (Tables 47.1 and 47.2).

Neurapraxic (first-degree) injury is an ischemic injury which may have segmental demyelination, but no interruption of the continuity of

Table 47.1 Historical classification of nerve injuries

Seddon	Sunderland (degree)	Mackinnon
Neurapraxia	I	VI degree
Axonotmesis	II	Mixed injury pattern
	III	
Neurotmesis	IV	
	V	

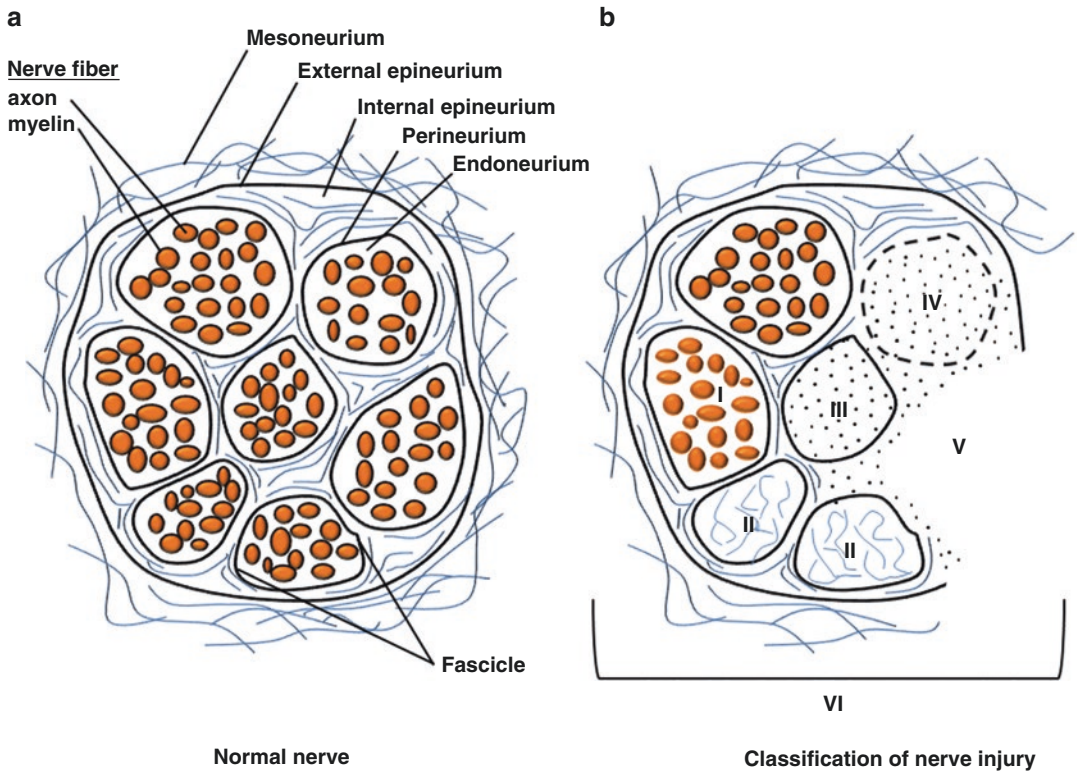

Fig. 47.3 Degrees of nerve injury. (**a**) Cross-sectional diagram of a normal nerve and its neural and connective tissue components. (**b**) Classification of nerve injury in a cross-sectional diagram. Normal nerve fascicle is found in the top left. First-degree (*I*) injury is neurapraxia with segmental demyelination. Second-degree (*II*) injury is axonotmesis that involves the axon and myelin. Third-degree (*III*) injury is injury to the axon, myelin, and endoneurium. Fourth-degree (*IV*) injury is neurotmesis with an injury to the axon, myelin, endoneurium, and perineurium. Fifth-degree (*V*) injury is a nerve that is not in continuity and is transected. Various normal and injury patterns within the nerve are considered sixth-degree (*VI*) injury

Table 47.2 Classification and management of nerve injuries

Degree of injury		Histological changes					Tinel's sign		Recovery	Rate of recovery	Surgical management
		Myelin	Axons	Endo-N	Peri-N	Epi-N	Present	Advancement			
I	Neurapraxia	+/–					–	–	Complete	Up to 12 weeks	–
II	Axonotmesis	+	+				+	+	Complete	1″ per month	–
III		+	+	+			+	+	Varies[a]	1″ per month	+/–
IV	Neuroma in continuity	+	+	+	+		+	–	None	None	+
V	Neurotmesis	+	+	+	+	+	+	–	None	None	+
VI	Mixed injury (I–V)	Various fibers and fascicles demonstrate various pathological changes					+	+/–	Some fascicles (II, III)	Depends on injury (I–V)	+

N neurium (e.g., *Endo-N* endoneurium)

[a]Recovery can vary from excellent to poor depending on the amount of scarring and the motor versus sensory axon misdirection to target receptors

axonal or connective tissue. A localized conduction block is present in this injury. Since the axons are not injured, recovery can be expected in up to 12 weeks with remyelination of axons. Tourniquet palsies are typically acute conduction blocks and recover within 12 weeks. In chronic nerve compression or radiation neuritis, a permanent conduction block may exist.

Axonotmetic (second-degree) injury is described by the disruption of axons, but with intact connective tissue sheaths. The axon segment distal to the injury undergoes Wallerian degeneration. In this type of injury, the connective tissue sheaths are uninjured and recovery will be complete with an expectant rate of nerve fiber regeneration of ~1 in. per month. The progress of regeneration can be followed by a Tinel's sign. However, motor recovery will be incomplete and adversely affected in circumstances where the distance from the nerve injury to the motor end plates results in prolonged denervation. In terms of management, first- and second-degree injuries are managed conservatively.

Axonotmetic (third-degree) injury is characterized by fibrosis in the endoneurium that prevents regeneration of some injured axons. This may lead to incomplete or mismatched end-organ innervation and may require decompression of scar tissue or areas of entrapment to optimize recovery. The recovery with decompression is uniformly better than that seen with a repair or graft reconstruction, unless it is associated with severe causalgia.

Neurotmesis (fourth-degree) injury represents an in-continuity neuroma with no potential for spontaneous recovery. The entire population of regenerating axons proximal to the injury is blocked by scar tissue. Neuroma excision with an end-to-end or graft repair is indicated in this type of injury. Neurotmesis (fifth-degree) injury is a complete transection of the nerve fiber which includes both axons and all connective tissues. This type of injury is the most severe and mandates surgical repair.

Sixth-degree injury describes nerve injuries demonstrating two or more degrees of injury at the same level of disruption. This injury pattern is the most challenging since it requires treating each injury pattern uniquely based on degree of injury. Reconstructions of these injuries require a high level of judgment and technical skill in order to protect and not downgrade uninjured fascicles or those that have recovery potential while reconstructing the fourth- and fifth-degree injury components.

Background and Considerations in Motor Nerve Reconstructions

For motor reconstruction, knowledge of the anatomy and physiology present at the muscle-nerve interface, in addition to the nerve itself, is critical in understanding and treating peripheral nerve injuries. The motor end plates provide the communication of the nerve to the muscle. Their presence is imperative; they are the adaptors that allow continuity of the circuit. Without the motor end plates at the neuromuscular junction, functional innervation is absent. In the normal state, there is a physiologic cycle of denervation and reinnervation occurring at the skeletal muscle, due to synaptic instability and axonal dropout. These transient periods of denervation are completely ameliorated by rapid reinnervation that follows. It is only with prolonged denervation that pathologic changes occur within the muscle [50].

In the setting of denervation, changes occur not only in the nerve but also in the newly denervated muscle, and this sequence of events is termed denervation atrophy. Immediately following nerve injury, proteases associated with the ubiquitin-proteasome pathway cause myofibril reabsorption, myosin and actin filament catabolism, decreased muscle cell size, and increased collagen deposition in the extracellular space. With prolonged time of denervation and increased loss of myofibrils, myocytes may undergo a process similar to apoptosis. These changes do not occur uniformly throughout the muscle, and fiber-type grouping may occur with reinnervation [50]. There is a loss of capillaries, which over time may result in large proportions of the muscle becoming avascular [6]. Simultaneously, the muscle environment is optimized for reinnervation. Acetylcholine receptors and neural cell adhesion molecules are upregulated diffusely across the muscle, a state similar to that in embryogenesis. These factors help to guide ingrowth of the motor axon, and once the regenerating nerve has reached the muscle target, a neuro-

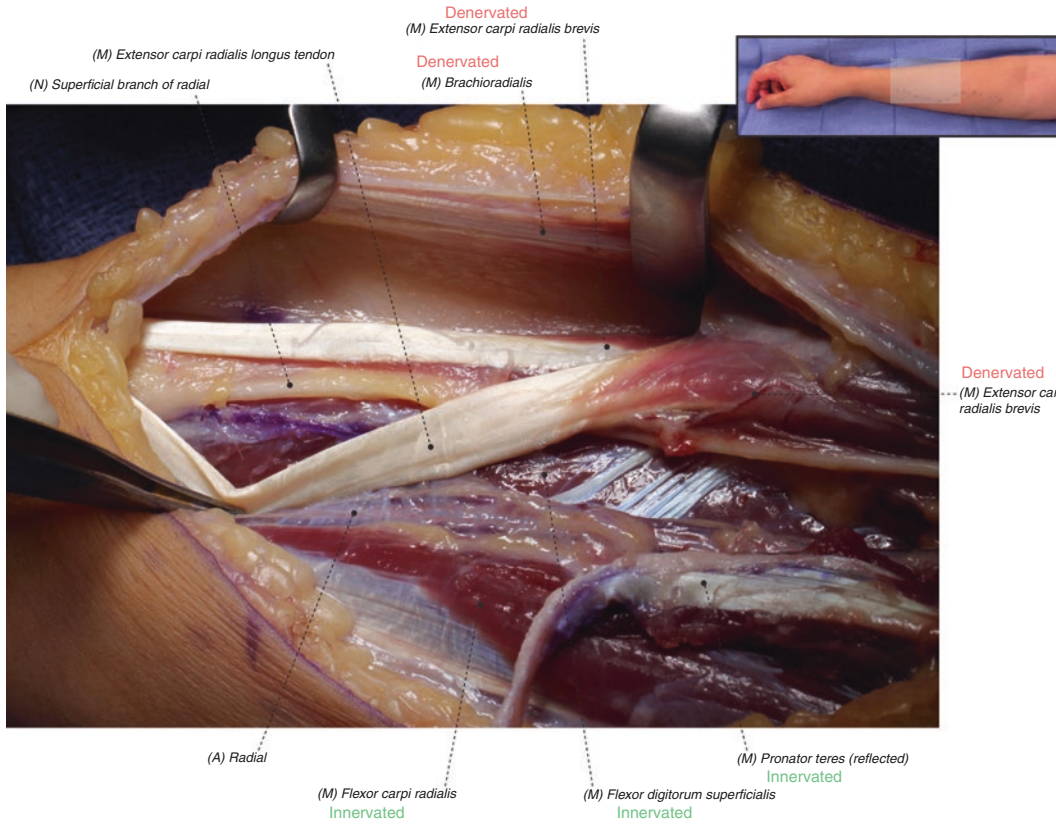

Fig. 47.4 Appearance of prolonged denervation in muscles. Denervated muscles atrophy as time elapses following nerve injury and take on a pale appearance with signs of fatty infiltration. This patient had complete radial nerve palsy following a humeral fracture, and a median to radial nerve transfer was performed 6 months following the injury. The radial-innervated muscles, specifically the extensor carpi radialis brevis, have a discolored appearance when compared to the functional median-innervated muscles following 6 months of denervation. (*N* nerve)

muscular junction is formed, and acetylcholine receptors and neural cell adhesion molecules are once again expressed only in the vicinity of the motor end plate [50]. With denervation atrophy, loss of muscle cross-sectional area corresponds with decreased contractile force, and with prolonged denervation, myofibril disorganization and collagen replacement result in decreased specific force capacity [45]. Unfortunately, deficits in specific force are permanent. With denervation, there is decreased muscle power, increased time to peak contractile force and to relaxation, and reduced speed of contraction [50].

Muscle reinnervation occurs following axonal regeneration, synaptogenesis, and resumption of contractile function. A reduction in the number of regenerating motor axons, however, results in deficits in muscle force [11, 50] as well as changes in gross appearance with pale color and significant atrophy (Fig. 47.4). With increasing periods of denervation, the embryonic-like state of high affinity between the regenerating nerve and muscle diminishes. Eventually, the muscle becomes refractory to synaptic formation; it can never be reinnervated, regardless of neuroregeneration. It is this time sensitivity to motor reinnervation that is integral to reconstructive planning for motor recovery. The location of the nerve lesion may preclude optimal or even feasible functional motor recovery via traditional methods. Denervation greater than 12–18 months is often considered the upper limit of this timeline depending on the patient's age. Proximal nerve lesions that are a long distance from their motor target may preclude primary muscle reinnervation given the known rates of neuroregeneration. If a nerve regenerates

in an adolescent at a rate of 1 mm daily, a lesion that is 50 cm from its motor target may have a diminished or absent functional result, particularly if time has passed since the onset of injury before presentation to the peripheral nerve surgeon.

Sensory reinnervation is not limited by such time constraints as motor end plates are not involved in sensation. Sensory reconstruction may be performed at any time and may traverse any distance due to the lack of time constraints.

Types of Pediatric Peripheral Nerve Injuries Specific to the Thorax

Pediatric peripheral nerve injury may result from numerous etiologies, as previously outlined. Specific to esophageal disorders and treatment, pediatric surgeons may encounter stretch injuries to the brachial plexus, phrenic nerve injury, brachial plexus tumors, brachial plexus birth-related palsy, positioning injuries with compression on the ulnar or peroneal nerves, thoracic outlet syndromes, intercostal neuromas and post-thoracotomy pain, and recurrent laryngeal nerve injury. One of the most devastating peripheral nerve injuries in children is injury to the brachial plexus. As this injury is more common than other etiologies of nerve injury at an incidence of ~1.5 injuries per 1,000 live births [18] and the majority of the pediatric peripheral nerve literature relates to this topic, many examples in this chapter will use this clinical problem. Brachial plexus injuries also clearly illustrate some of the challenges in peripheral nerve reconstruction: proximal injuries that are far from their end targets, nerve gaps, and loss of critical function.

History of the Treatment of Pediatric Nerve Injuries

Pediatric peripheral nerve injuries have been described since antiquity. Albrecht Durer, a German painter of the Renaissance, depicts the classic waiter's tip position of the arm that is characteristic of Erb's palsy in two of his famous works, one being in an infant [84]. Brachial plexus injury related to birth trauma is one of the more common pediatric peripheral nerve injuries and was first described by William Smellie in 1768 [91]. Wilhelm Erb described paralysis of C5 and C6 in 1874 [16], but it wasn't until 1903 that the first operative treatment for birth-related brachial plexus palsy was reported by Kennedy. His technique involved neuroma excision and direct suture repair of the ensuing nerve defect via immobilization of the head to the shoulder to facilitate nerve coaptation. He describes three cases and recovery of arm abduction and elbow flexion in the patient with longest follow-up (9 months) [65]. Reports of disappointing results following operative intervention for obstetrical brachial plexus palsy in the early twentieth century [42, 63] led to a period of nonoperative management for many decades. After brachial plexus injury, the resultant muscle imbalances and abnormal mechanics may lead to growth inequities, bony deformities, joint contractures, and osteopenia. The advancement of microsurgical techniques as well as improved understanding of neural anatomy and pathophysiology brought a renewed interest in operative intervention for pediatric brachial plexus injuries in the 1970s. Multiple classification systems of injury have since been proposed, and a plethora of literature exists describing suggestions for improved techniques, optimal surgical timing, and methods of enhancing regeneration.

Management of Peripheral Nerve Injuries

The modern approach to treatment of peripheral nerve injuries in children is similar to that in adults and is based upon the classification of the injury. Knowledge about the natural history of nerve injuries is important to prevent unnecessary interventions, provide patient education, and optimize outcomes. Classification of the injury, therefore, is an important initial task in the management of pediatric nerve injuries. Sunderland described five degrees of nerve injury [72], and Mackinnon emphasized a sixth degree, as outlined in an earlier section. First- through third-degree nerve injuries are typically managed without surgical intervention as they demonstrate

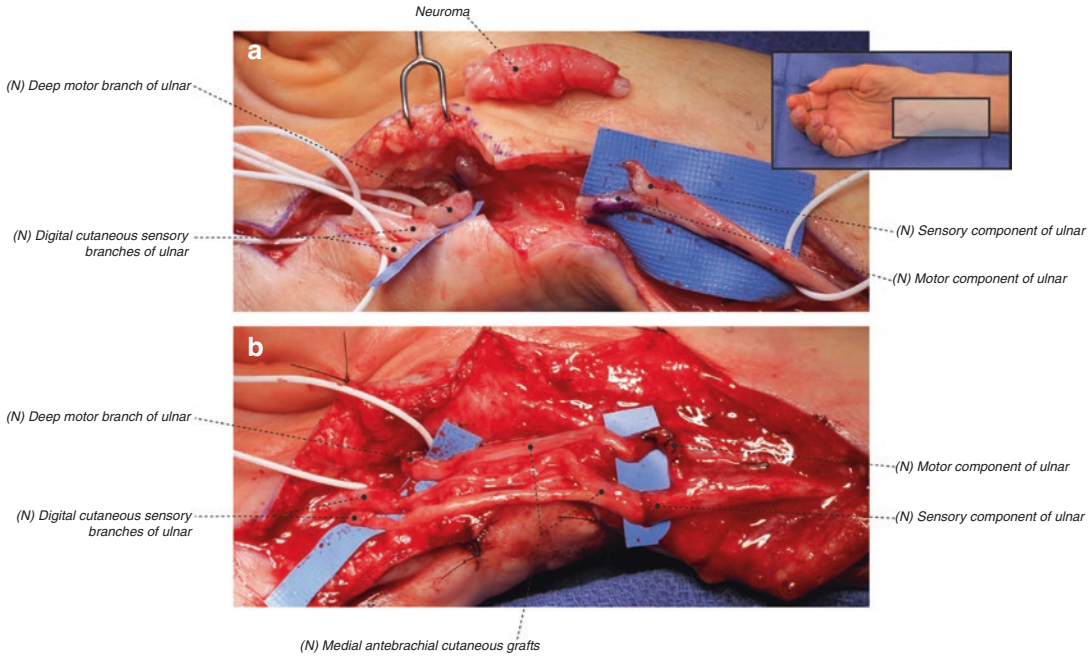

Fig. 47.5 Tension-free nerve repairs and matching motor/sensory modalities are essential concepts for successful nerve reconstruction. (**a**) The removal of a failed primary nerve repair introduced a large ulnar nerve defect. (**b**) The large ulnar nerve defect was reconstructed with three medial antebrachial cutaneous (MABC) cable nerve grafts. A single MABC graft was used to reconstruct the deep motor branch. Two MABC grafts were used to reconstruct the superficial sensory branches. Tension-free repairs occurred with modality and fascicular alignment. (*N* nerve)

complete or near complete recovery. Occasionally third-degree injuries may demonstrate incomplete recovery and may require surgical intervention to optimize results. Fourth- and fifth-degree injuries, however, will not spontaneously recover and do require surgery for optimal recovery. Sixth-degree nerve injuries represent a mixed picture, and the need for surgical intervention depends on the specific involved injury and recovery over time (Table 47.2). Physical examination is paramount, but electrodiagnostic studies may also provide useful information regarding the level of injury. Other imaging modalities, such as diaphragmatic ultrasound or MR myelogram, may augment diagnosis in specific cases.

The goals of nerve reconstruction are to provide restoration of function in as safe, complete, and rapid manner as possible while minimizing any donor site morbidity. To achieve these goals, reconstructions must be appropriately planned and performed using meticulous surgical technique. Nerve coaptations should always be without tension (Fig. 47.5). Nerve grafting is preferable to direct coaptations performed under tension or apposition via postural modifications. In addition, the injury should be clearly identified. Elegant nerve reconstructions performed within the zone of nerve injury have no functional value.

Management of peripheral nerve injuries may involve options such as behavior modification, nonoperative supportive management, decompression, neurolysis, primary repair, excision of lesion and interpositional nerve grafting, tendon transfers, joint fusion, stimulation, and nerve transfers. The specific technique used is dependent upon multiple factors including the location of the injury; the distance from the target; the presence of associated injuries including life-threatening or systemic disease or injury, adjacent vascular injuries, or complex soft tissue wounds; the time since the injury occurred; and the availability of donor tissues. The specific algorithms for treatment selection have been previously described [12, 38, 71, 82] and are not the focus of this review.

The outcomes of peripheral nerve reconstruction also depend on a multitude of factors, including patient characteristics, type and location of the injury, timing of intervention, and type of repair performed. An area that consistently demonstrates disappointing results involves injuries that occur distant from their end target. These reconstructions are typically performed with nerve grafting. The operations are lengthy, require donor nerves, and may require several years to achieve only modest recovery. The main explanation for suboptimal results relates to the time required for neuroregeneration to reach the target. Often motor end plates are lost and sensory recovery is delayed. In addition, the reconstruction may be limited by the amount of expendable nerve graft that is available. These are several of the challenges that have limited functional outcomes in peripheral nerve reconstruction for decades, and it is because of these limitations that new techniques have been developed.

Theory and Principles of Nerve Transfer

Nerve transfer offers an alternative approach to nerve reconstructions that otherwise may result in suboptimal function utilizing traditional techniques. Nerve transfers utilize redundant, expendable innervation to convert a more proximal injury to a more distal injury, one that is close to the end target. The specific functional deficit is identified and reconstructed. In a recent meta-analysis comparing treatment of adult upper trunk brachial plexus injuries with nerve transfers or nerve grafting, improved functional results for elbow flexion and shoulder function were noted in the nerve transfer group [23]. Nerve transfers dramatically decrease the time necessary for motor and sensory reinnervation, thus preventing loss of motor end plates, speeding recovery, and providing improved functional outcomes.

Indications for nerve transfer include proximal nerve injuries, an inadequate proximal nerve stump (thereby rendering traditional nerve grafting impossible), unacceptable time for regeneration (either due to distance to target or delayed presentation), and scarring that would prohibit safe dissection at the zone of injury. Nerve transfers permit dissection away from the site of original injury, in a field of unscarred tissue that facilitates ease and perhaps quality of the reconstruction. In addition, nerve transfers allow reconstruction of function without downgrading any regenerating function that exists, such as in the setting of sixth-degree nerve injuries.

Increased knowledge of internal nerve topography has facilitated the technique of nerve transfer. Laboratory studies have also demonstrated the safety of internal nerve dissection permitting the delicate isolation of specific nerve fascicles [14]. Nerve transfers require the availability of redundant, expendable donor nerves near the site of the denervated target (motor end plates or sensory receptors). For example, in the setting of a proximal ulnar nerve injury, traditional nerve grafting would result in little to no recovery of intrinsic motor function of the hand. Distally, however, the AIN branch to pronator quadratus can be transferred to the deep motor branch of the ulnar nerve to optimize motor recovery [60, 94]. Intraoperative electrical stimulation is used to confirm nonfunction of the injured nerve and to delineate motor targets of specific nerve fascicles in the potential donor to ensure redundancy prior to harvest. Donor sensory fascicles must innervate noncritical regions of sensation. Donor nerves should be purely motor or purely sensory depending on the function being reconstructed. Ideally donor nerves possess functional synergy to the function being reconstructed, similar axon number, and an appropriate size match. Unlike tendon transfers, nerve transfers are appropriate in the setting of joint stiffness. Motor and sensory reeducation is critical in the postoperative period to optimize function [12, 19, 71, 83, 94]. Several nerve transfers are now regularly utilized by our group and are summarized in (Table 47.3).

End-to-Side Nerve Transfer

A specialized type of nerve transfer is the end-to-side (ETS) technique. ETS nerve transfer is a technique where the distal end of a transected injured (recipient) nerve is reinnervated by coapting it into the side of an intact functional (donor)

Table 47.3 Nerve transfer options for various injured nerves in the upper extremity

Injured nerve	Impaired function	Donor nerve	Recipient nerve
Restoration of motor function			
Spinal accessory	Shoulder elevation and abduction	Medial pectoral, C7 fascicle	Spinal accessory
Long thoracic	Scapula stabilization, forward abduction	Medial pectoral, thoracodorsal, intercostal	Long thoracic
Suprascapular	Shoulder abduction, external rotation	Branch of spinal accessory	Suprascapular
Axillary	Shoulder abduction	Medial triceps branch of radial, medial pectoral	Deltoid and teres minor branches of axillary
Musculocutaneous	Elbow flexion	FCU fascicle of ulnar, FCR/FDS fascicle of median	Biceps brachii and brachialis branches
Triceps brachii	Elbow extension	FCU fascicle of ulnar, thoracodorsal	
Radial	Wrist and finger extension	FCR, FDS ± PL	ECRB branch and PIN
Pronator teres	Forearm pronation	FCU, FDS, FCR, ECRB	Pronator teres
AIN	FDP finger flexion, thumb flexion	Brachialis, FDS, supinator, ECRB	AIN
Median	Thumb opposition	AIN (pronator quadratus branch)	Recurrent (thenar) branch of median
FPL	Thumb flexion	FDS	FPL
Ulnar	Hand intrinsics	AIN (pronator quadratus branch)	Motor component of ulnar (DMBU)
Restoration of sensory function			
Median (C5, 6)	C5, 6 distribution	3rd webspace fascicle of median	1st webspace fascicle of median
Median	1st, 2nd, 3rd webspace, median palmar aspect of hand	Dorsal cutaneous branch of ulnar	1st webspace fascicle of median
Ulnar	Ring and small finger, dorsal and ulnar palmar aspect of hand	3rd webspace fascicle of median	Sensory component of ulnar
Radial sensory	Radial aspect of hand	LABC	Radial sensory

FCU flexor carpi ulnaris, *FCR* flexor carpi radialis, *FDS* flexor digitorum superficialis, *PL* palmaris longus, *ECRB* extensor carpi radialis brevis, *PIN* posterior interosseous nerve, *AIN* anterior interosseous nerve, *FPL* flexor pollicis longus, *DMBU* deep motor branch of ulnar nerve, *LABC* lateral antebrachial cutaneous nerve

nerve (Fig. 47.6). This technique was first described in the late 1800s and subsequently reintroduced in the early 1990s as published reports in peer-reviewed literature [49, 52, 56, 57, 88, 89]. Since then, the clinical use of the ETS nerve transfer has been a controversial topic in peripheral nerve surgery [57, 81, 96] due to the numerous contradictory studies.

On review of the literature, there are two concepts related to ETS nerve transfer and axonal sprouting: "regenerative sprouting" and "spontaneous collateral sprouting" [61]. The first, "regenerative sprouting," describes the concept where axons reinnervating the recipient nerve are derived from sprouts of regenerating units in response to axonal injury. This concept of sprouting with injury is widely accepted in the community. However, the second concept of "spontaneous collateral sprouting" is the source of controversy. This concept describes axons collaterally sprouting spontaneously without injury from the nodes of Ranvier.

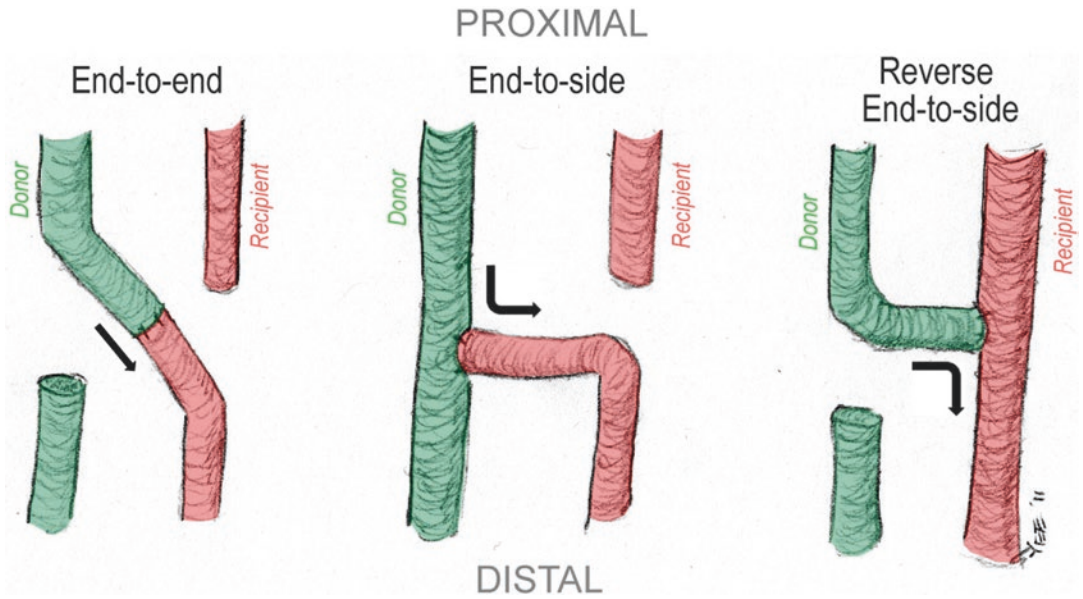

Fig. 47.6 Types of nerve transfer coaptations. Three nerve transfer coaptations currently exist: end to end (ETE), end to side (ETS), and reverse end to side (RES). ETE is the standard coaptation for restoring critical function and directing the maximum number of fibers from donor into recipient nerve. ETS is the distal segment of the recipient nerve being coapted to the side of the donor nerve. RETS is the proximal end of the donor nerve being coapted to the side of the recipient nerve. The *arrow* describes the direction of nerve regeneration

Some studies have shown evidence that suggests ETS nerve reconstruction results in collateral sprouting in sensory nerves [8, 25, 30, 77, 78]. This phenomenon is seen in patients recovering sensation over time following a donor nerve harvest that results in a sensory deficit. By contrast in motor nerves, there is evidence that motor axons will sprout only if injured [30]. Clinically, this specific phenomenon is seen in our hypoglossal-facial experience and in a specific nerve transfer for shoulder reconstruction [70]. Even if the donor nerve requires an axotomy injury, this may not significantly impact its function due to the redundancy and plasticity of donor nerve motor end plate innervation [27, 30, 61, 66–69].

The ETS nerve transfer may be a viable reconstructive alternative in specific circumstances where other reconstruction options are unavailable. These circumstances can include restoration of noncritical sensation, donor sensory nerve deficits, and select motor injuries where an axotomy injury to facilitate regenerative sprouting in the donor nerve will not cause a significant motor deficit. In the situation of a motor reconstruction, an ETS nerve repair is essentially a form of nerve transfer where axons are diverted through a modest neurectomy within a single fascicle of the donor nerve. The size of the neurectomy determines the amount of regenerative sprouting while limiting the donor deficit. Clinically, we have reported functional motor recovery after an ETS nerve transfer [70] and continue to utilize this technique in a specific shoulder reconstruction. In this report, a compression injury is made proximal to the coaptation site in addition to the axotomy to facilitate a regenerative nerve front. For sensory reconstruction, the ETS nerve repair occurs via a perineural window in the donor nerve. The size of the perineural window dictates the amount of collateral sprouting [93].

Another situation where ETS nerve transfer may be clinically relevant is in the context of harvesting donor sensory nerves and neuropathic pain. Dorsi et al. [13] describe two possible sources of neuropathic pain in nerve injuries: neuroma for-

mation of the distal end of the proximal nerve and collateral sprouting from adjacent sensory territories into the distal injured sensory nerve (Fig. 47.7). While neuroma pain is managed with neuroma resection and proximal intramuscular transposition, hyperalgesia pain from collateral sprouting can be managed with an ETS nerve repair. The theory is that by providing regenerative nerve fibers to innervate the distal portion of the injured sensory nerve, collateral sprouting at the source of hyperalgesia pain is prevented. We have seen these techniques successfully manage injury-induced neuropathic pain.

Reverse End-to-Side Nerve Transfer

Another special technique of nerve transfer is the reverse end-to-side (RETS) reconstruction. In a RETS nerve transfer, an expendable donor

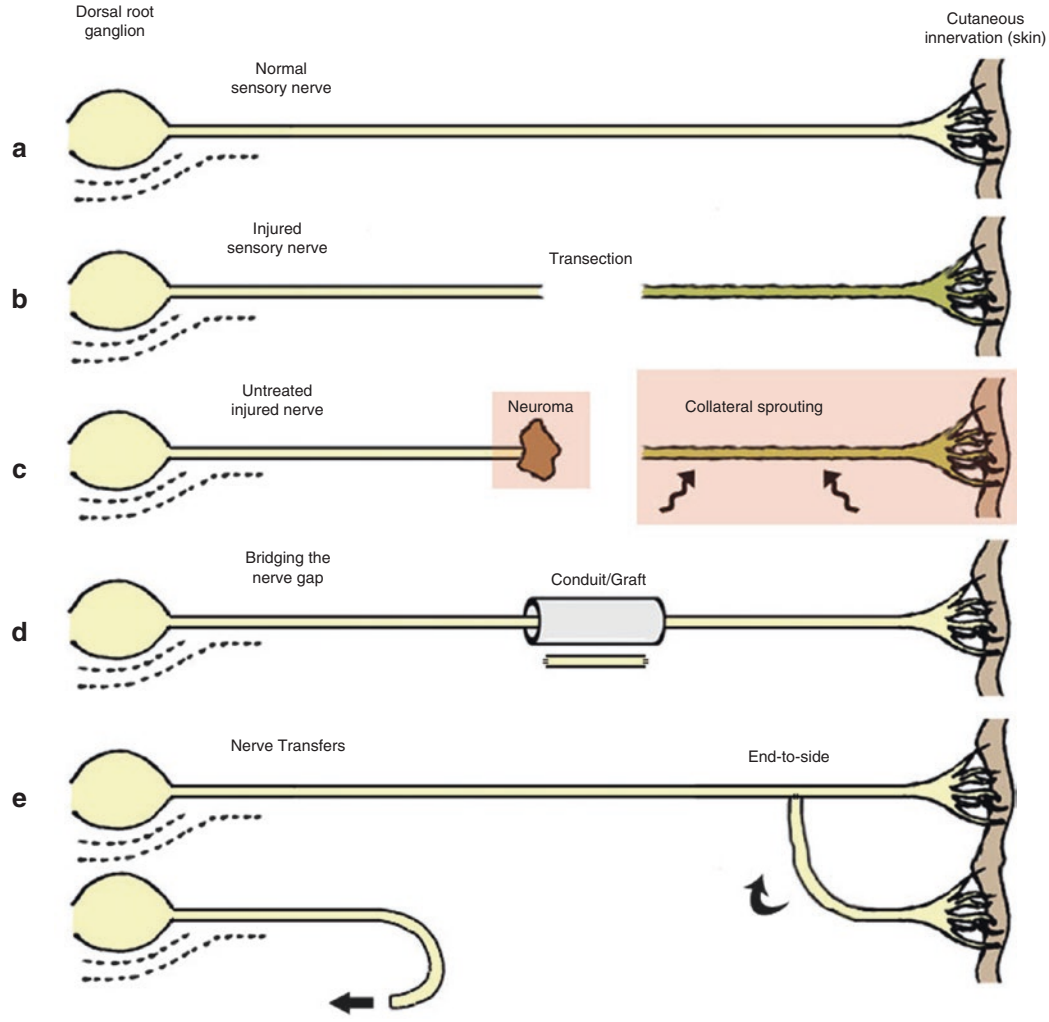

Fig. 47.7 Strategies for pain management from neuroma formation and hyperalgesia. Pain related to nerve injury can originate from two sources: neuroma formation at the distal stump and hyperalgesia due to collateral sprouting form adjacent sensory territories. (**a**) Normal sensory nerve. (**b**) Injured sensory nerve with transection injury and Wallerian degeneration in the distal nerve segment. (**c**) Pain resulting from neuroma formation and collateral sprouting. (**d**) One type of strategy is to bridge the gap with a graft or conduit. (**e**) Another strategy is to transpose the proximal end of the nerve into the muscle to prevent neuroma formation. An end-to-side nerve transfer into an adjacent sensory nerve is performed to prevent hyperalgesia

nerve is transected distally, and the distal (donor) end is transferred to the side of the intact injured nerve close to the target muscle via a perineural window (Fig. 47.6). The advantages of the RETS nerve transfer are to provide additional motor axons to "supercharge" the regenerating nerve as well as provide early muscle reinnervation (preventing loss of motor end plates) by "babysitting" the target muscle until the native axons regenerate from proximally.

In the case of significant proximal nerve injuries that occur distant from the target muscle with minimal to no chance of functional recovery, an end-to-end motor nerve transfer can be used to restore prompt motor reinnervation [10, 12, 74, 83]. The appropriate surgical management for nerve injury distant from the target muscle, however, is less clear. In this scenario, the expected functional recovery after traditional nerve grafting techniques is fair, but not excellent, as functional recovery from nerve regeneration is dependent on the relationship between the time elapsed from injury and the distance to the target muscle [83]. This scenario is also considered to be a "gray area" between proximal and distal injuries where indications for distal nerve transfers or primary repairs are less clear. RETS nerve transfer may serve as a technique to approach this type of scenarios and achieve optimal results.

Published data on RETS nerve transfer are relatively scarce. Isaacs et al. (2008) described successful donor motor axon regeneration through a RETS coaptation resulting in successful target muscle reinnervation, but dependent upon injury to the recipient nerve with resultant muscle denervation [37]. Fujiwara et al. [21] later augmented a primary repair with the RETS nerve transfer and found improved motor and sensory functional recovery in RETS augmentation than transection and repair alone. Finally, Isaacs et al. [37] performed a similar study in the tibial and peroneal nerves except with the addition of preferential electrical stimulation. They demonstrated significant target muscle reinnervation in both the donor and recipient native nerves. Although these studies provided supportive evidence for the RETS nerve transfer, they lacked reliable negative controls of injury without repair. The importance of this negative control addresses the superlative regenerative capacity of the rodent model and prevents a false positive [9]. This is an important consideration in the rodent model when translating to humans with slower regenerative capacity.

Recently, Kale et al. [43] published a study from our institution that presents a model of RETS that comprehensively evaluates the surgical technique in a rodent. This study boldly suggests that the RETS technique can result in an equivalent number of donor motor axons as the standard end-to-end (ETE) nerve transfer. This finding is supported by fluorescent microscopy results (Fig. 47.8). Potentially, these results suggest that in the clinical setting, the RETS nerve transfer could replace the ETE nerve transfer in cases where any potential for native axonal regeneration exists. However, further investigation is ongoing to determine the mechanism and utility of the RETS nerve transfer.

To further describe the utility of the RETS nerve transfer, Kale et al. [43] also presented in their study a case report of a successful reconstruction of an ulnar nerve deficit following a failed ulnar nerve transposition. The patient presented with a 4-month history of severe ulnar nerve deficit following failed transposition, which included intrinsic hand wasting. He was reconstructed by revision of the ulnar nerve transposition and augmentation with the RETS anterior interosseous to ulnar motor nerve transfer. Twelve months postoperatively, he has recovered excellent ulnar intrinsic function, which is unseen in revision ulnar nerve transposition cases, as results are typically fair. Due to this excellent clinical finding, we have adopted the RETS nerve transfer to augment recovery of ulnar intrinsic muscles after ulnar nerve injury secondary to recurrent cubital tunnel syndrome. On several occasions, we have seen early recovery within months postoperatively and excellent intrinsic muscle recovery long term. Essentially for these ulnar nerve case scenarios, we are creating a Martin-Gruber anastomosis in the distal forearm.

Our encouraging results with RETS in the adult population have prompted its use in appro-

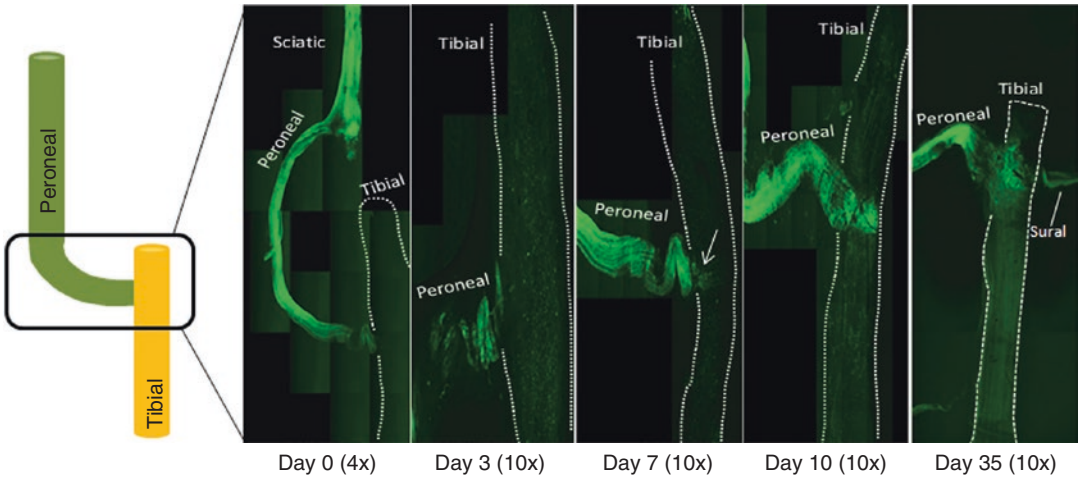

Fig. 47.8 Confocal imaging of the reverse end-to-side nerve transfer coaptation site. The schematic (*left*) displays the area of interest for the composite images acquired with confocal microscopy (*right*). Axonal infiltration across the reverse end-to-side coaptation was noted as early as 7 days after surgery in the rodent model (*white arrow*). Regeneration into the recipient distal tibial nerve stump was robust 35 days after surgery. An adjacent sural side branch is seen in the 35th day image. *Dotted lines* outline the tibial nerve (Reprint from Kale et al. [43], with permission from Elsevier)

priate clinical scenarios in the pediatric population as well. We were called to assist intraoperatively with an iatrogenic phrenic nerve injury during thymectomy to treat refractory myasthenia gravis in a 16-year-old female. Appropriate exposure was obtained via a right anterior thoracotomy (Fig. 47.9a). Although we were expecting the injury to require a nerve graft (Fig. 47.9b), a tension-free primary suture coaptation was achieved after extensive mobilization of the phrenic nerve (Fig. 47.9c). Because the injury was over 7 cm proximal to the diaphragm (Fig. 47.9d), the RETS technique was used to supercharge diaphragmatic innervation from the sixth intercostal nerve. The neurovascular bundle to the sixth intercostal space was dissected intrathoracically (Fig. 47.9e). An epineurial window was made in the phrenic just proximal to the diaphragm; the sixth intercostal nerve was then transected and coapted to the phrenic at the epineurial window (Fig. 47.9f). The patient has recovered well, now 5 months postoperatively, and reports less shortness of breath compared to her preoperative state, which may be related to the myasthenia treatment. The theory, again, was to attempt to preserve the motor end plates to the diaphragm and decrease the time to motor reinnervation.

Another application of the RETS technique in our clinical pediatric practice is reconstruction of the deep motor branch of the ulnar nerve in a 9-year-old female, 5 months after she sustained a proximal radius and ulnar fracture that was managed nonoperatively. The patient had noted immediate numbness in the ulnar nerve distribution at the time of the fracture. She had ongoing sensory recovery, but wasting of the intrinsic muscles. Electrodiagnostic studies were consistent with ulnar neuropathy. At the time of ulnar nerve decompression in Guyon's canal at the wrist, intraoperative electrical stimulation of the deep motor branch demonstrated no motor function. The deep motor branch was then reconstructed with the pronator quadratus branch of the anterior interosseous nerve in a RETS fashion. At 10 months postoperatively, the patient has regained normal intrinsic hand function, indicating complete motor reinnervation of the muscles innervated by the deep motor branch of the ulnar nerve (Fig. 47.10). The distal reconstruction was able to preserve the motor end plates in the ulnarly innervated intrinsic hand muscles to improve the functional outcome.

Nerve Transfer Outcomes

The concept of nerve transfer was proposed as early as 1913 [32]. With increased reports of the shortfalls of traditional reconstructive techniques in certain clinical scenarios, as well as the difficult application of allotransplantation, nerve transfers have become increasingly utilized and accepted.

Nerve transfer outcomes in adults have been reported extensively in the literature [7, 15, 92]. Due to increasing popularity of this technique in recent years, results from the adult population no longer have to be extrapolated to the pediatric

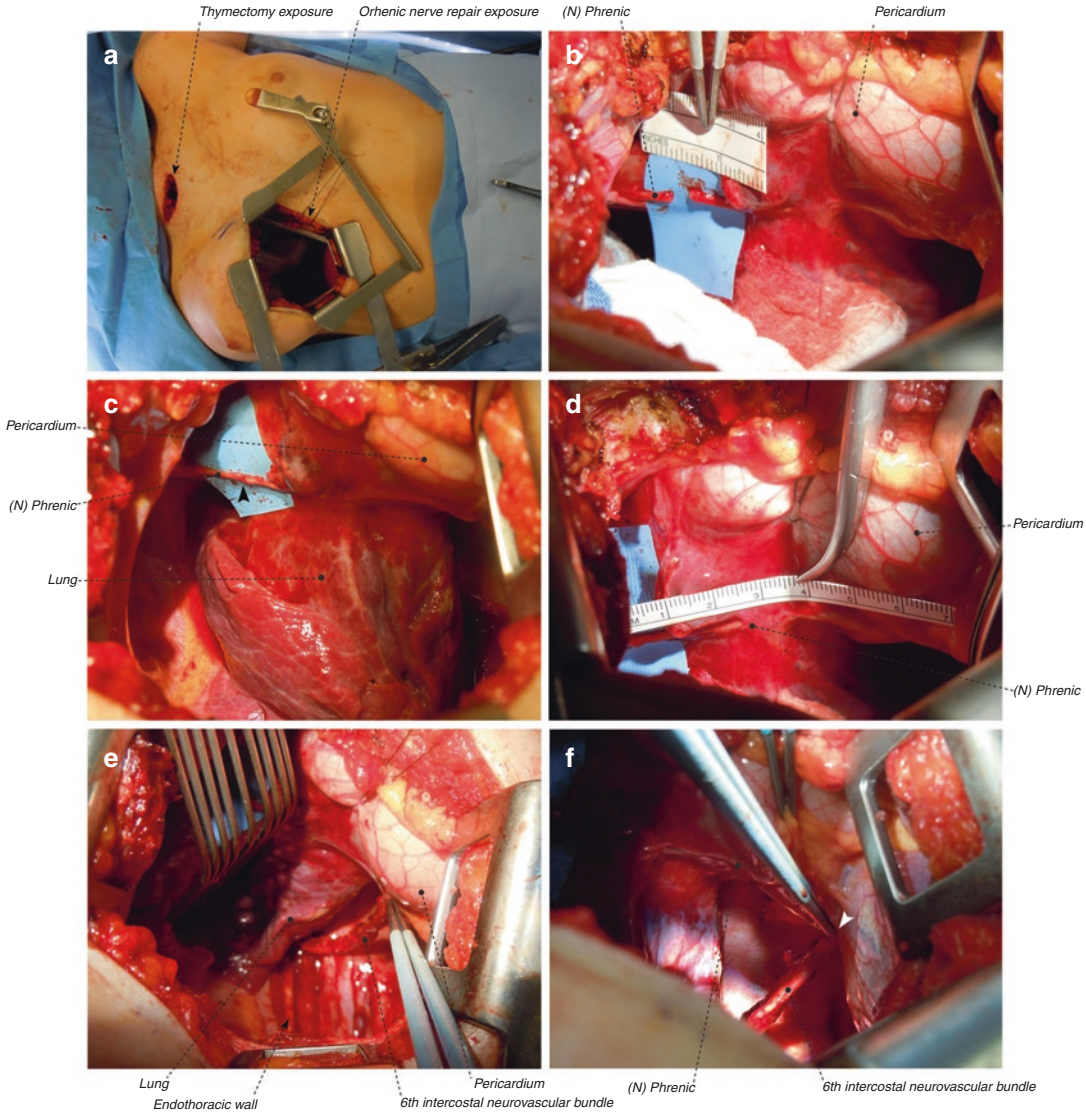

Fig. 47.9 Reverse end-to-side (RETS) sixth intercostal to phrenic nerve transfer following an iatrogenic phrenic nerve injury. (**a**) The phrenic nerve was injured during thymectomy to treat myasthenia gravis in the neck exposure. A right anterior thoracotomy was performed to access the phrenic nerve for the RETS nerve transfer. (**b**) The phrenic nerve was found completely transected. (**c**) A tension-free repair was completed on the phrenic nerve. (**d**) The injury occurred 7 cm from the diaphragm. (**e**) As result, the sixth intercostal neuromuscular bundle was harvested. (**f**) Following, the sixth intercostal nerve was transferred via RETS technique to the phrenic to augment the proximal primary repair. (*N* nerve)

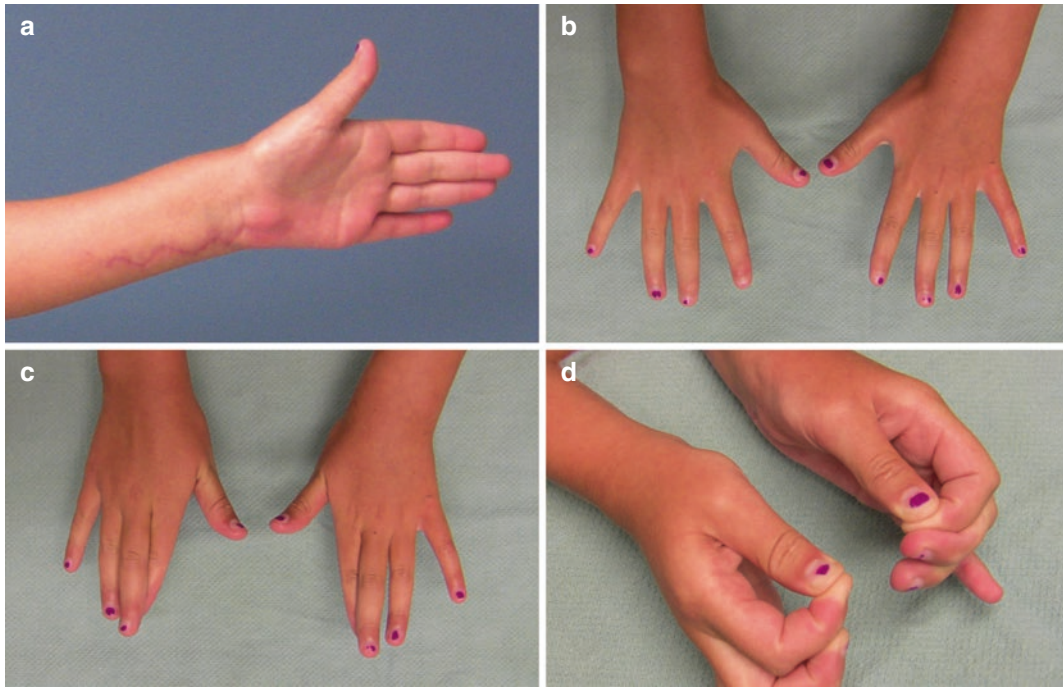

Fig. 47.10 Outcome following reverse end-to-side (RETS) anterior interosseous to ulnar motor nerve transfer. A nine year-old female sustained proximal radius and ulnar fractures and demonstrated ulnar nerve injury with wasting of ulnar intrinsic muscles and loss of ulnar nerve sensation. While she showed sensory recovery, the RETS anterior interosseous to ulnar motor nerve transfer was performed to augment the proximal motor nerve regeneration to her ulnar intrinsic muscles. (**a**) Ten months post-operative results showed significant recovery of ulnar intrinsic muscles. Her incision is well-healed. (**b**) Significant wasting is not seen in the left hand. (**c**) The patient was able to cross her fingers. (**d**) The patient did not display Froment's sign

population. Outcomes after nerve transfer in the pediatric population have been encouraging. Much of the reconstructive focus has been to reestablish biceps function. After transfer of two to three intercostal nerves to the musculocutaneous nerve for biceps reinnervation in patients with birth-related brachial plexus palsy, Kawabata et al. [44] reported 84 % of the patients achieved M4 biceps strength. They noted that recovered strength diminished with increasing age at the time of surgery. Two different groups have reported good to excellent results after performing Oberlin's transfer (ulnar nerve FCU fascicles transferred to nerve to the biceps) in pediatric patients. Al-Qattan [58] reported restoration of normal biceps function in two of two patients 5 months after transfer. Noaman et al. [59] noted recovery of good to excellent biceps function in five of seven children who had undergone an Oberlin transfer. Blaauw and Slooff [5] described outcomes after a series of 25 patients had undergone medial pectoral nerve transfer to the musculocutaneous nerve for restoration of biceps function in the setting of brachial plexus palsy. They noted complete reinnervation of the biceps muscle in most cases by 6 months after surgery. Over a mean follow-up of 70 months, 17 patients achieved excellent function and 5 patients displayed fair function. There were two complete failures due to disruption of the coaptation. They noted their selection of the medial pectoral nerve due to its increased number of motor fibers compared to intercostal nerves. Reconstruction of external shoulder rotation has also been applied to the pediatric population. Pondaag et al. [64] performed suprascapular neurotization to achieve infraspinatus reinnervation either by grafting of C5 or accessory nerve transfer. Their results showed only 17 of 86 patients (20 %) recovered greater than 20° of external shoulder rotation, and 41 % of patients were incapable of any shoulder rotation, regardless of the type of reconstruction performed. They did not,

however, dissect the suprascapular nerve to the level of the suprascapular notch, and this could be a confounding factor. They did note that patients compensated well to effectuate good function. Improved results were seen when the spinal accessory nerve was transferred to the suprascapular nerve in children who had spontaneously recovered shoulder and arm function, except for shoulder external rotation, following birth-related brachial plexus injury. Functional exorotation was achieved in 52 of 54 children, and external rotation exceeded 20° in 39 of 54 patients. Shoulder abduction also improved in half of the patients [85].

Conclusions

While pediatric peripheral nerve injuries are relatively uncommon, their effects can be life-altering. Treatment options continue to evolve as knowledge regarding the anatomy, topography, and physiology of the peripheral nervous system matures, as do technology and approaches to restoring function. In recent years, nerve transfers have improved previous shortcomings of our treatment armamentarium. Injuries that are far from the end target can be managed more efficaciously by converting them to a distal reconstruction, borrowing expendable nerves to reestablish critical function. This not only speeds reinnervation, thereby preserving motor end plates and improving function, but also allows reconstruction of previously untreatable lesions or of patients who have a delayed presentation. In addition, reconstruction away from the site of initial injury may provide for a safer outcome for the patient in cases of extensive scarring near important structures. Critical outcomes analysis and scientific endeavors will continue to progress the treatment of pediatric peripheral nerve injuries.

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Tracheomalacia and the Effective Aortopexy

48

John E. Foker, Abby C. Meyer, and Frank Rimell

Introduction

A soft trachea (tracheomalacia) is susceptible to collapse, creating variable degrees of ventilatory distress and producing symptoms from the barky cough common in esophageal atresia (EA) patients to life-threatening difficulties in breathing. The symptoms are roughly proportional to the severity of the tracheomalacia (TM) and range from increased work of breathing, stridor, wheezing, failure to thrive, recurrent pneumonias, severe respiratory distress, apnea, bradycardia, cyanosis, to sudden ventilatory arrest [1–7].

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Many tissues and organs, such as muscle and bone, react to stress, pressure, and other biomechanical stimuli with hypertrophy and increased density to counteract these forces. The trachea and bronchi, however, do not strengthen to resist external and internal pressures, but, rather, lose the tissue components which produce structural rigidity. Collapse can then occur with the negative intraluminal pressure of inspiration or from forces and structures external to the trachea during expiration, usually the innominate artery and its origin off the aorta.

TM, as a result, is found in a variety of conditions including EA and certain types of congenital heart disease, most notably the absent pulmonary valve syndrome or with vascular rings which put external pressure on the airway [1–13]. In EA, the frequently large upper pouch puts pressure posteriorly on the trachea, compressing it against the innominate artery, likely causing the tracheomalacia [13]. As a result, both the cartilage and myoelastic elements do not have normal structural rigidity. When the upper pouch does not have a decompressing fistula, it will be larger and more likely to produce significant tracheomalacia.

The pressure can also come from vascular structures such as enlarged pulmonary arteries or an entrapping vascular ring [8, 9]. Again, the external pressure almost paradoxically causes weakening of the cartilage and the tendency to collapse. TM may also be produced by prolonged intubation while on the ventilator [7, 14]. Consequently, pressure either

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from outside the trachea or from within will decrease tracheal structural rigidity [7, 14]. In addition, primary TM may occasionally occur without apparent etiology.

The seriousness of TM in some cases has led to increasing awareness of the condition and advances in diagnostic techniques and treatment in children [5, 7, 15–17] (see Chap. 46). As suggested by the variation in signs and symptoms, TM exists in a spectrum of severity, and the mode of treatment will depend on the clinical consequences. Recently a classification of TM severity as determined endoscopically has been proposed based on the amount of collapse and loss of luminal area. This classification, with experience and refinement, may prove useful [18].

For mild cases, treatment begins with good nutrition, adequate calcium supplementation, and removal of the stimuli producing the TM. With time, the trachea should firm up and improve the situation. Ideally, this will be sufficient, but it may not be and an operative procedure will be needed. Whatever the treatment selected, good nutrition and a positive calcium balance which would include vitamin supplements should be emphasized as part of the regimen.

With more significant TM, the symptoms become more severe as does the difficulty breathing. At the severe end of the spectrum, TM can interfere substantially with ventilatory mechanics and produce apneic episodes, a form of an acute life-threatening event (ALTE). Because air hunger quickly leads to increased inspiratory and expiratory efforts with more collapse, the patient's condition may quickly deteriorate and lead to a near death experience or even become fatal (see Chap. 46). For these patients, an effective operative treatment would prevent significant collapse, and its value would be easily justified.

The situation for the intubated patient with TM is more complicated, and the decision must be made whether to move toward weaning and eventually attempt extubation or accept the much slower process of tracheal firming while still intubated. With an indwelling tube, the trachea may have difficulty in stiffening up and progress will be very slow. Effective surgical treatment (an aortopexy) may however greatly hasten extubation and, with it, discharge from the hospital despite persistence of the TM.

Operative Approaches for Tracheomalacia

Several operative approaches have been described beginning with the first solution used: a tracheostomy and indwelling tube to prevent collapse. A tracheostomy and cannula, however, bring a number of undesirable consequences and should only be done in the most difficult of circumstances and will not be considered further here. Another approach has been to firm up the trachea internally by stents or externally by cartilage grafts [19, 20]. The former method is prone to severe complications, and the latter, although elegant, is difficult and involved technically. Consequently, the most commonly used operative solution is the aortopexy, the simplified name which often includes additional vessels besides the aorta. An aortopexy does not treat the TM directly but prevents collapse by elevation of any vessels impinging on the trachea anteriorly. In some cases, fixation of the posterior extent of the trachea and even the tracheal membrane itself posteriorly to the prevertebral fascia will allow the anterior vessel elevation to more effectively round up the trachea and prevent collapse. Which components of the aortopexy will be used will largely be determined by bronchoscopy. Primary collapse of the trachea itself will increase the importance of the anterior elevation of the vessels, while encroachment of a redundant posterior membrane may make adding fixation valuable to the aortopexy.

The majority of patients with significant tracheomalacia also have anomalies of the esophageal atresia spectrum. With only the "barky cough" of the typical post-repair EA patient, nothing further will need to be done, and the situation will improve with time. For significant TM, however, with severe difficulties in breathing and near coaptation seen endoscopically, an aortopexy is typically done to round up the trachea and hinder collapse. In these cases, the innominate artery is usually the offending vessel, with variable contributions by the neighboring area of the aorta and the pulmonary arteries. The aortopexy may also include elevation of these vessels to obtain adequate relief as determined by the bronchoscopy findings. When the trachea is very soft and the tissues between it and the innominate artery are not

strong enough to insure the trachea is adequately rounded up, the rings themselves may also need to be suspended to prevent collapse.

For tracheobronchomalacia from cardiac causes, operative treatment includes removing the deleterious pressure effects of the impinging vessels and also rounding up the trachea to limit collapse with expiration and inspiration by some variation of an aortopexy [8, 9, 11, 21]. The absent pulmonary valve syndrome, as will be discussed, is probably the congenital heart defect that is best known to produce TM [9]. Vascular rings if present are divided and the arteries rotated or elevated away by the aortopexy sutures. Vascular rings may also be associated with tracheal stenosis, but, in many cases, only TM may be the result.

For infants having significant acute spells or requiring ventilator support and intubation because of TM, serious consideration should be given to an operative solution. Carefully done, an aortopexy has a considerable potential to eliminate or, at least, greatly reduce the severity of these spells at a low risk. For patients on the ventilator primarily because of TM, the benefit will likely include a relatively quick extubation and removal from the ventilator, ending the deleterious consequences and considerable expense of being ventilator bound or ending up with a tracheostomy.

Principles of an Aortopexy

For the recommendation of an aortopexy, the TM symptoms should be considered a significant problem and deserving of operative treatment. For infants without significant vascular anomalies such as the EA/TEF patient, the vessels, including the innominate artery, are normal in position and size, and it is the soft trachea which cannot resist the presence and pressure of the artery as well as the excursions of the mediastinum. Because of the TM, the presence of the artery collapses the airway enough to set up the possibility of cycles of increasing difficulty breathing with the consequent air hunger producing more vigorous ventilatory efforts with additional tracheal collapse. For these cases of severe TM with apparent vascular compression of the airway, the operation will necessarily have two considerations. First, the arteries producing the vascular compression are moved, and second, if the TM is severe enough, the trachea itself must be rounded up by elevation anteriorly and fixation posteriorly if the relief of the vascular impingement does not produce the desired effect.

The direction of compression can be lateral as well as in the anterior-posterior plane. Examples of lateral tracheal compression and tracheomalacia include vascular rings, large pulmonary arteries, and even a descending aorta that is displaced medially and pushed anteriorly by the vertebral bodes [8–10]. For these patients, systematically removing the different components of vascular compression is part of the operative treatment. The effect of the various maneuvers can be determined by directly observing the result through the bronchoscope during the effective aortopexy procedure that will be described.

Several aortopexy approaches have been described in the literature with differing incision sites and, therefore, varying views of the offending vessels with some differences in effectiveness and durability of the procedure. The operations have included both open and thorascopic techniques and the differences also affect the end result.

Our operative procedure, which will be described in detail, gains access to the upper mediastinum with the patient slightly head-up with the neck extended and supine with bronchoscopy available to evaluate the result. The innominate artery and, if necessary, other arteries (e.g., pulmonary arteries, branches of the aorta) will be pulled forward by sutures into the wall of the vessel and anchored into the posterior fascia of the sternum and proximal portions of the ribs. The vessels that need to be elevated will vary and the aorta will not always be included.

It must be emphasized that no dissection is carried out between these vessels and the tracheobronchial tree so that these tissues serve to pull the anterior surface of the airway forward. It is also important to not dissect behind the trachea so that tissue holds the posterior wall of the airway in place when the anterior wall is pulled forward and the trachea is rounded up. These form the basic principles of an effective aortopexy.

The Vessels Producing the Airway Compression

Typically in the EA patient who has a left aortic arch, it is the innominate artery crossing over the mid to lower portion of the trachea that is the principal offending collapsing the soft airway. As noted, other vessels may be involved particularly when there are also vascular anomalies in the area or in the presence of congenital heart disease. The complexity of the vascular structures and impingement may vary considerably as will the degree of TM. As detailed, an analysis of the vessels and the structures impinging on the airway as necessary should be carried out by scan (CT or MRI) and echocardiography. Bronchoscopy during the aortopexy will be of most value as it will reveal the requirements of an effective operation. Direct elevation of the vessels during the procedure will allow the effects to be observed.

The effect of the innominate and neighboring arteries can be demonstrated by several methods; however, we have relied on bronchoscopy to definitively reveal the location and degree of obstruction at the time of aortopexy. This method of assessment has the considerable advantage that the area of collapse is revealed and the effect of the aortopexy can be directly determined. Pulling forward the innominate artery as well as its aortic origin should round up the trachea and allow visualization of the main stem bronchi. With the benefit confirmed, the elevation of the vessels can be secured and the operation completed.

Aortopexy Operations

Several techniques for an aortopexy have been described [1, 7, 9, 21–34]. The important consideration in the aortopexy is to bring the vessels forward in an even way so that the elevation rounds up not only the central portion of the airway but also keeps open both main stem bronchi. Whether or not this is accomplished depends, at least in part, on the incisional site. The trachea and proximal bronchi are in the midline directly in back of the sternum. If the incision for the aortopexy is either to the right or left of the sternum, the elevation on that side will be satisfactory although it may be at the expense of the lumen of the opposite main stem bronchus. The far side cannot be easily reached by a right- or left-sided approach, and compression of the opposite main stem bronchus may not be relieved and possibly even made worse by the aortopexy. All of the lateral approaches have this potential shortcoming, and, at the end of the procedure, bronchoscopy with the patient supine should be done to assess the consequences for the opposite main stem bronchus.

Commonly cited operative approaches utilize right or left anterior thoracotomies or an incision through the bed of the third rib. In some techniques, Dacron patches or tissue flaps are also used to enhance the aortopexy and even do away with the aortic sutures [24, 29]. A minimally invasive technique has also been used approaching from either the right or left intercostal area. For these thoracoscopic approaches, the same caveats pertain about achieving a symmetrical aortopexy. The less graceful suture placement and the large needles used in thoracoscopic procedures, moreover, would seem to make the risk of bleeding greater [32, 33]. Certainly, it seems apparent to the thoracoscopic surgeon that the risk is greater; consequently, the stitches are few, are placed more superficially, and are more likely to pull out, and symptoms recur [32].

To address the asymmetrical elevation that may occur with either a right- or left-sided approach, a manubriotomy through a low collar incision was used which allowed direct access into the anterior mediastinum [34]. This provided equivalent exposure to the partial sternotomy approach, made a symmetrical elevation of the vessels possible, and produced an effective result. Simple sutures were placed in the superior aspect of the aortic wall without pledgets, however, which might make them more prone to pull through. Finally, a full midline sternotomy has been used in two cases, but a complete sternal split is unnecessary and certainly enlarges the operation [31].

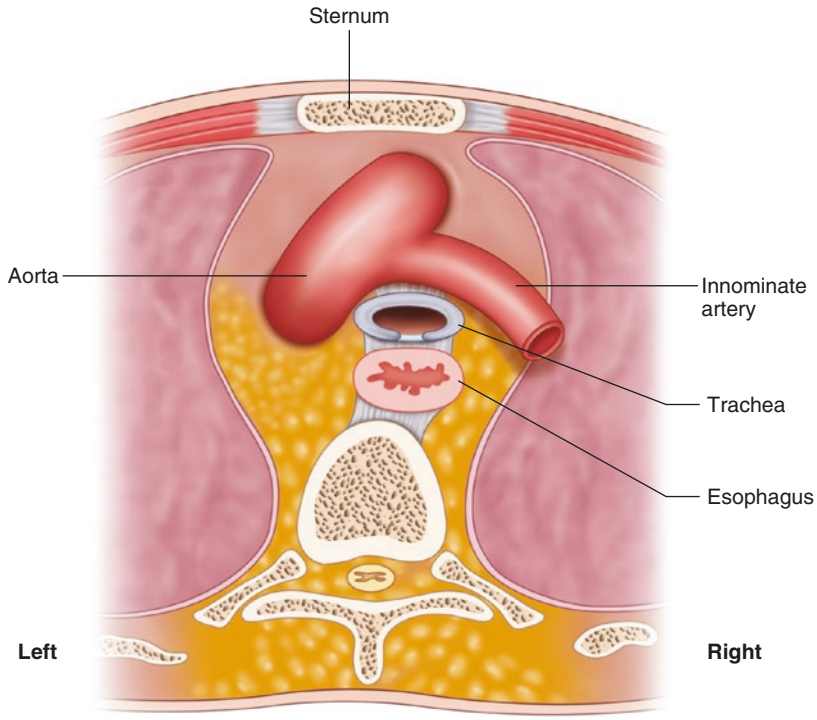

Fig. 48.1 Elevation of the vessels. The partial sternotomy approach provides direct exposure of the innominate artery, ascending aorta, and the main pulmonary artery. In most cases, the innominate artery courses across the soft trachea and becomes a significant contributor to the airway obstruction. Elevation of the innominate artery and, to some degree, the right-hand side of the upper ascending aorta relieves the obstruction by rounding up the trachea making it no longer subject to collapse. In other approaches to an aortopexy, simple sutures are typically placed through the anterior high point of the upper ascending aorta and then to the back of the sternum resulting in a rounding up of the trachea and relief of symptoms. If the approach is either from the right or left, there are several potential drawbacks to this method. If bleeding occurs, it may be difficult to reach and control. By the partial sternotomy approach, the vessels are directly accessible, and, if bleeding occurs, it can be more directly controlled. Also, from a more lateral approach, the elevation of the aorta may not be straight anterior and may roll somewhat to the opposite side and tends to be impinged on the main stem bronchus if the elevation is not even and favors the side of the approach. With the patient supine and the use of intraoperative bronchoscopy, the consequences for both main stem bronchi can be readily seen, and if they are still impinged upon, then elevation of the pulmonary artery and/or the pericardium itself should relieve the problem. Elevation is accomplished by placing pledgeted horizontal mattress sutures on the lateral aspect of the innominate artery and the ascending aorta as shown. The sutures are then placed in the posterior sternal fascia, and the effect of elevation can be readily determined by bronchoscopy. If bleeding occurs, the suture can be removed and the site controlled with an additional U-shaped suture

An Effective Aortopexy

The Operative Approach

In order to fulfill the basic principles of the operation and address some of the problems which arise with the procedures cited, we have used a limited midline approach to provide excellent access and facilitate an effective aortopexy. A short transverse incision is made slightly above the manubrial-sternal angle (Fig. 48.1). A low collar neck incision could also be made in the skin lines; however, it will require a somewhat longer opening for equal access to the anterior mediastinum [32]. The manubrium is split in the midline which allows direct access to the thymus and the vessels lying beneath it (Fig. 48.2). The bony incision is readily made and gentle, and

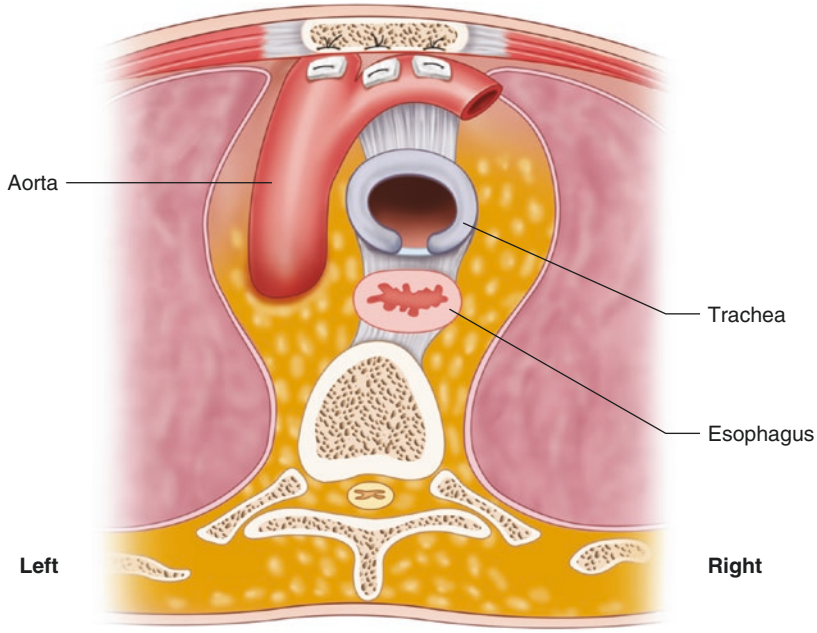

Fig. 48.2 A short (3 cm) transverse incision is made at the level of the manubrial-sternal junction. A partial sternotomy beginning at the sternal notch is carried down to just past the junction which will provide very adequate exposure. The right lobe of the thymus can be moved, or removed if necessary, which will reveal the upper part of the pericardium. A vertical incision in the pericardium and tacking the edges apart laterally will reveal the ascending aorta, innominate, and main pulmonary artery. This exposure, along with simultaneous bronchoscopy, will allow the effects of elevating the innominate artery and neighboring portion of the ascending aorta to be determined. If necessary, the pulmonary artery or the pericardium itself can be elevated. This information will allow for both a more precise placement of the sutures and effective aortopexy to be accomplished

progressive spreading with a small sternal retractor provides excellent exposure. Surgeons will utilize the incisions with which they are familiar and most pediatric surgeons have done few, if any, sternotomies. Most have access to colleagues, however, who are familiar with this approach and could provide help in carrying out the partial sternotomy.

Once the partial sternotomy has been made, the two lobes of the thymus are easily separated, and retraction or removal of one lobe reveals the innominate artery and the upper part of the ascending aorta. If needed for an effective aortopexy, the main and branch pulmonary arteries are also readily accessible and can be elevated [9]. Whether or not one opens the upper portion of the pericardium will depend on what is needed to complete the aortopexy although it does enhance the exposure.

A very important advantage of this approach is the ability to use bronchoscopy during the procedure to accurately assess the effect of the elevating sutures. With the patient lying flat, the endoscopist can see the airway without distortion and will be able to assess the effect of elevating the arteries on the trachea and both main stem bronchi. Initially, the likely offending vessels can be gently elevated with pickup forceps and the effect observed.

This operative approach provides even greater advantages when dealing with more extensive tracheobronchomalacia and more complex causes of compression by vascular abnormalities. In addition to elevating the innominate artery, the more proximal ascending aorta, pulmonary arteries, and even the pericardium itself can be brought anteriorly to round up the lower trachea and proximal main stem bronchi [8, 9]. The upper portion of the pericardium overlies the lower trachea and proximal main stem bronchi, and, therefore, elevation may be useful in opening these airway structures. Pulling upward on the pericardium at various points will allow the effect

to be determined via the bronchoscope and the permanent site for the sutures determined.

For some cardiac anomalies (e.g., absent pulmonary valve syndrome), the vascular abnormalities are usually repaired at the same time. In this case, the very large main pulmonary arteries which appear to be the cause of the tracheobronchomalacia would be reduced in size by reefing them up after the intracardiac repair is completed [9]. Before closure of the incision, elevating the pulmonary arteries will insure the airway is adequately rounded up. On rare occasions, elevating the superior and lateral aspect of the pericardium itself may also be useful to extend the effect of the aortopexy to include the main stem bronchi. Finally, if the trachea does not round up satisfactorily by elevating the vessels, monofilament sutures in each side of the anterior surface of the tracheal rings can be used to open the lumen.

Another maneuver that may provide help in EA patients following repair where there is no esophagus directly in back of the trachea is to tack the ends of the tracheal rings or even the posterior membrane directly to prevertebral fascia. Care must be taken with suturing the posterior membrane, however, to avoid an air leak. In addition, because the approach will usually be from the right side, the left main stem bronchus may not be opened adequately, and determining the effects of these sutures by bronchoscopy will be more difficult with the patient in the lateral position.

The Arterial Sutures

The arterial sutures are pledgeted to provide holding power and are placed in a horizontal mattress fashion on the lateral aspect of the vessels and then into the posterior fascia along each side of the sternum (Figs. 48.3). At this point, the sutures can be pulled up and the degree of relief of compression of the trachea and bronchi assessed.

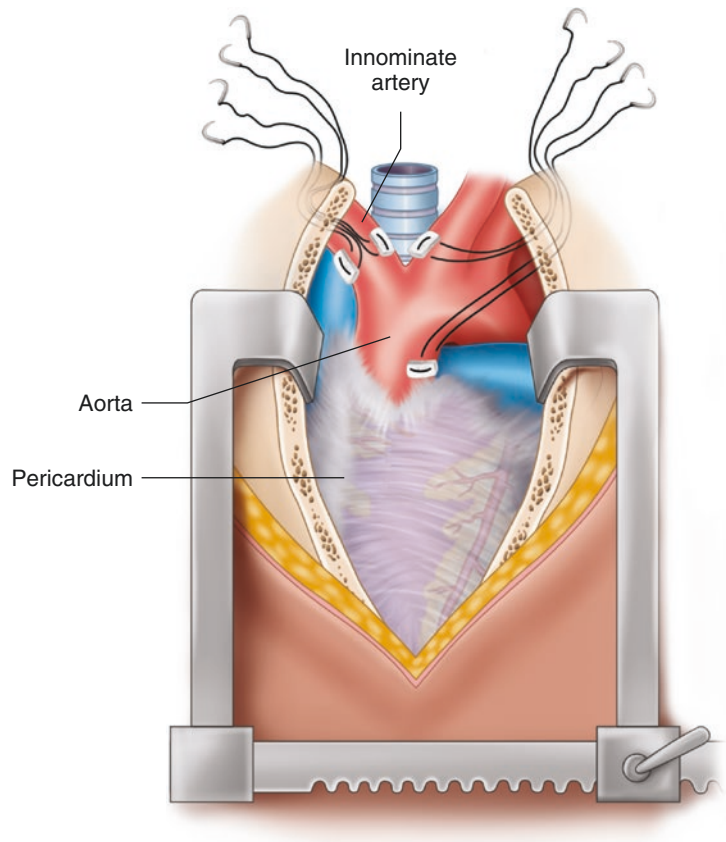

Fig. 48.3 The arterial sutures are pledgeted to provide holding power and are placed on the lateral aspect of the vessels and then into the posterior fascia along each side of the sternum

The sutures are carefully placed within the wall of the vessels while not entering the lumen. Because of the upward force on these sutures and vessels, if the lumen is entered, it would seem prudent to remove the suture and repair the vessel with a more superficially placed 6-0 or 7-0 Prolene suture if there is still bleeding. The suture material itself can either be a braided permanent polyester suture such as 4-0 or 5-0 Tevdek which has good strength and is mounted on a relatively small needle. A permanent monofilament such as Prolene could also be used and small pledgets fashioned and mounted on the suture. Either 4-0 or 5-0 monofilament suture will slide through the tissues of the vessel wall easily be amply strong. More care has to be taken, however, in the handling of the more brittle monofilament suture.

The sutures are then passed through the posterior fascia of the manubrium and sternum. Pledgets are usually not needed on this end because these tissues are sturdy. At this point, a small chest tube is brought up through the subxiphoid area and into the pericardial space just inferior to the elevating sutures. One or two sternal wires are placed and the ends tagged. A small piece of very fine silastic sheeting is cut to size and placed centrally between the back of the manubrium and overlying the vessels that will be elevated. The thin silastic sheeting will make a future sternotomy incision, if needed, easier and safer to accomplish. The sternal edges are then drawn together by the wires as closely as convenient to still allow tying of the elevating sutures. When this is done, the sternal wires are twisted together, and the remainder of the closure is carried out in the usual fashion.

This operative approach fulfills the basic principles of an effective aortopexy, and if more extensive elevation is required in complex cases, it can be accomplished. An important consideration is that because the elevation begins centrally and moves laterally along the course of the main stem bronchi, as needed, there will be no secondary kinking of these structures as might happen if they are relatively out of view of the surgeon and bronchoscopist.

Results

Aortopexy was first described by Filler et al. [1] and used initially to treat TM in EA patients. As with most operations, the approach and technical details have evolved and, presumably, improved with time. Our institutional experience began primarily with cardiac patients with varying degrees of secondary tracheobronchomalacia. Because a sternotomy was also utilized in these patients, a partial midline reopening created no additional problems. Moreover, because of the severity of the tracheobronchomalacia, bronchoscopy was often used which made clear the utility of being able to directly determine the effects of the aortopexy.

The EA population requiring aortopexy has grown steadily and includes patients referred for EA growth procedures, those with continuing tracheobronchomalacia problems, or following a failed aortopexy which has compromised the opposite main stem bronchus. The results reflect our increased understanding of the principles behind an effective aortopexy.

Very early on, three cases of severe TM with cardiovascular anomalies had a tracheostomy. Two of the tracheostomies were done before the referral for aortopexy, and the one done after this operation was because of continuing severe cardiac dysfunction. In our EA series, no patient has required a tracheostomy for TM and the only tracheostomy done was in a patient referred with bilateral recurrent laryngeal nerve damage and failed EA repair.

Recently a comparison of nonrandomized cases at another institution showed the partial sternotomy approach was more effective in relieving symptoms than thoracotomy or thorascopic approaches [7]. Furthermore, recurrence was very unusual presumably because of the more accurate suture placement under direct vision.

The aortopexy, as described, has proven very effective and, as opposed to the placement of a stent(s) or even a tracheostomy, should not produce later problems that may be difficult to solve. Consequently, we believe it can be recommended in cases with documented, significant TM, typically causing severe ventilatory problems and certainly for those experiencing near

death episodes (ALTEs). Because of the considerable benefit and low risk, this procedure has been requested when less extreme but still very stressful symptoms are present. Noisy breathing from tracheal collapse indicates a critical airway narrowing which will tolerate little further reduction in the opening as might occur during an upper airway viral infection. Certainly, it is difficult to predict when moderate ventilatory distress will quickly cycle into a significant apneic episode. For parents who have witnessed difficulty breathing and progression to apneic episodes in their babies, it will be very reassuring to have this problem effectively treated.

Summary

An aortopexy will be more likely to be effective, we believe, if the principles described are followed. A short upper sternal incision as described will reveal the offending vessels and allow them to be elevated in a symmetrical fashion without leaving a main stem bronchus comprised. The suspension of the vessels which cause the compression will round up the very soft tracheobronchial tree, and this can be confirmed by intraoperative bronchoscopy. If the cause of compression is more complex, a wider range of elevation using multiple sutures to other great vessels or even the pericardium can be easily carried out through this incision. Finally, if bleeding occurs, the vessels are well exposed and accessible. With this overall approach, the symptoms should be greatly reduced or eliminated and without later consequences for the patient's growth and development.

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Thoracoscopic Aortopexy

49

Klaas(N) M.A. Bax

Introduction

Aortopexy was first described by Gross and Neuhauser in 1948 [1]. Gross used it for the treatment of tracheal compression what he and his radiologist Neuhauser thought was caused by an anomalous innominate artery. Much later Mustard et al. and Berdon et al. queried an abnormal origin of the innominate artery as the cause of the compression [2, 3]. They felt that the trachea was compressed by a normally placed innominate artery in the relatively "overcrowded mediastinum" of a small child. They thought that perhaps a degree of tracheal softening also played a role. In 1976 Filler et al. described three children with life-threatening events due to innominate artery compression after repair of esophageal atresia with distal fistula [4]. Slowly it was understood that rather an intrinsic abnormality an extrinsic compression of the trachea caused tracheal obstruction in the majority of patients after esophageal atresia repair [5]. Nowadays the term tracheomalacia (TM) is used and aortopexy has become the procedure of choice for the treatment of severe forms of TM [6].

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Physiopathology

TM refers to a weakness of the trachea. The normal intrathoracic trachea dilates somewhat during inspiration and narrows with expiration as a result of differences between the intrathoracic and intraluminal pressures [7, 8]. In TM, this physiologic process is accentuated. The majority of cases of tracheomalacia are intrathoracic in nature; hence during expiration and particularly forced expiration or coughing, intrathoracic pressure is positive and the affected segment of trachea or bronchus narrows leading to wheeze [9]. In the less common case of cervical, extrathoracic TM, the collapse takes place during inspiration by transmission of the negative intrathoracic pressure, causing stridor. In esophageal atresia with distal fistula, there is a deficiency of cartilage, an increased width of the posterior membranous trachea, and an increased internal tracheal perimeter [10]. Malformed tracheal cartilage rings have also been found in the adriamycin tracheoesophageal fistula rat model [11]. In contrast to esophageal atresia with distal fistula, clinically important TM is rare in pure esophageal atresia [12], H-type tracheoesophageal fistula without atresia, and their combination [13].

In idiopathic TM or TM associated with compression, structural changes are less obvious but a decreased cartilage to muscle ratio seems common [14, 15]. Similar changes may be seen in children with sudden infant death syndrome [14].

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It has been questioned whether such an enlargement of the trachea is a congenital or acquired event. The same applies to TM in adults [6].

TM may be localized to one portion of the trachea or may involve the entire trachea. The main stem bronchi may be involved as well in which case the term tracheobronchomalacia is applicable. The terms tracheomalacia and tracheobronchomalacia have been used interchangeably especially in studies regarding children [6]. Isolated weakness of the bronchi, bronchomalacia, is much rarer. In this chapter the term TM is also used to include tracheobronchomalacia.

Classification

There are different classifications of TM. Some authors classify TM on a basis of the extension into localized and extensive forms [16]. Others make a difference between primary and secondary malacia. For Benjamin primary TM comprises premature infants, otherwise normal children, and children with dyschondroplasia, while secondary TM comprises children with tracheoesophageal fistula, children with innominate artery compression, and children with compression due to a vascular ring, a congenital cyst, or a tumor [15]. Austin and Ali make a distinction between congenital and acquired forms, but consider TM in association with compression by anomalous great vessels as acquired [9]. Carden et al. make the same distinction and describe a long list of potential causes in both groups. They include TM in prematures in the congenital form, but consider TM associated with congenital anomalies of the great vessels as acquired. They also place TM associated with congenital cysts like bronchogenic cysts, enterogenic cysts, cystic hygroma, lymphatic malformations, and tumors like teratomas in the acquired group [6]. TM associated with bronchopulmonary dysplasia should not be part of the primary congenital form as bronchopulmonary dysplasia in the premature is caused by damage due to long-term endotracheal intubation and mechanical ventilation with volume and barotrauma. As stated earlier, many authors do not believe in tracheal compression by an abnormal origin of the innominate artery; they rather believe in an intrinsic weakness of the trachea [2, 3, 6, 15, 17–19]. Whether there is a cause effect relationship between aortic arch anomalies and tracheal softening is speculative. More likely are both expressions of one event.

Mair and Parsons proposed a major airway collapse classification MAC system based on histopathologic, endoscopic, and clinical findings of the flaccid airway [20]. MAC 1 represents congenital tracheal collapse without external compression; MAC 2 represents tracheal collapse caused by external compression, e.g., vascular anomalies, cysts, tumors, and thymic or thyroid gland enlargement; MAC 3 refers to acquired TM arising from prolonged ventilation, tracheotomy, or severe tracheobronchitis. They felt that the term TM should be reserved for cases with widening of the posterior wall with a ratio to the anterior cartilaginous wall of 2:1 (Table 49.1).

Incidence

The incidence of TM is not commonly reported. One study estimated it to be 1 per 1,445 infants [21]. In a retrospective study of 664 bronchoscopies in a university setting, 15,4 % of the children studied had TM [22]. In another retrospective study of 512 bronchoscopies, the incidence of primary airway malacia was estimated to be 1 in 2,100 children [23]. In the subgroup of children with idiopathic TM, 46 % had TM, 36 % tracheobronchomalacia, and 16 % bronchomalacia. In children under the age of 3 years, scheduled for bronchoscopy due to a history of recurrent respiratory distress, the incidence of TM seems double [20]. In a study of 50 infants with TM, ± 50 % had primary TM. Most of the children with secondary TM were premature babies requiring prolonged mechanical ventilation [22]. TM is becoming much more frequently recognized [6, 9], which is undoubtedly related to an increased awareness among clinicians and the better imaging techniques. The better the diagnostic tools, e.g., multidetector CT [24] and magnetic resonance imaging [25], the higher the incidence is likely going to be.

Table 49.1 Classification

Primary
Idiopathic (otherwise normal children)
Associated with other congenital anomalies
Esophageal atresia with distal tracheoesophageal fistula
Congenital tumors or cysts
Anomaly of the great vessels
Double aortic arch
Right aortic arch
Aberrant innominate artery
Aberrant right subclavian
Anomalous left pulmonary artery
As part of a syndrome or association
Antley-Bixler syndrome
Blackfan-Diamond syndrome
Brachman-de Lange syndrome
Campomelic syndrome (skeletal)
CHARGE syndrome (coloboma, heart, atresia of choanae, retardation of growth, genital hypoplasia, earanomalies)
Chondrodysplasias
Deletion 11p13, 12q, 22q11
DiGeorge syndrome
Ehlers-Danlos syndrome
Hallermann-Streiff syndrome (skeletal)
Kniest dysplasia
Larsen syndrome (skeletal)
Mucopolysaccharidoses (Hurler, Hunter)
Pfeiffer syndrome
Pierre-Robin sequence
Translocations 18–22
Trisomies 9 and 21
VACTERL association (vertebral, anorectal, cardiac, tracheal, esophageal, renal, limb anomalies)
Williams-Campbell syndrome (congenital bronchiectasis)
Secondary (previous normal trachea)
Prolonged intubation/ventilation
Tracheostomy
Tracheobronchitis
Polichondritis
Trauma
Secondary compression
Abscess
Left atrial hypertrophy
Tumor including goiter, thymic enlargement

Modified from Carden et al. [6]

In children with esophageal atresia with distal fistula, TM is invariably present as is witnessed by the barking noise that those children make during forced expiration [26].

Natural History

As TM may be part of many underlying conditions, a general prognosis regarding TM itself is difficult to give. In most patients with TM, however, symptomatology is mild and intervention is not required. Many references state that symptoms improve with age and that symptoms often resolve by 1 or 2 years of age [6]. Most references are, however, old. In a study regarding 17 patients with primary bronchomalacia, all improved with time but the three patients over 5 years of age reported limitation of vigorous exercise indicating that pathology does not disappear completely with time [27]. A lifelong decrease in exercise intolerance in idiopathic TM has also been suggested by others [23]. In TM associated with esophageal atresia with distal fistula, the typical cough persists throughout adulthood [28]. TM may cause significant morbidity. It may go unrecognized or may be misdiagnosed as asthma or other respiratory conditions [6]. Moreover non-diagnosed TM has been implicated in the pathogenesis of sudden infant death syndrome [14, 29, 30]. There is an important subgroup of patients, who present with life-threatening symptoms requiring immediate treatment. In esophageal atresia with distal fistula, this is estimated to represent between 10 % and 20 % [12, 30]. Several factors have been implicated in the acute life-threatening events. Tracheal obstruction during expiration is certainly one of them, but reflex apnea caused by irritation of the trachea by acid secretions and/or a bolus of feeding in the esophagus has also been suggested as a contributing factor [4, 15]. Gastroesophageal reflux is common both in idiopathic TM [31, 32] and in esophageal atresia [26, 33]. Gastroesophageal reflux seems an important cause of acute life-threatening events in children even without esophageal atresia [34]. Compression of the trachea by a bolus of feeding

in the upper esophagus has also been implicated in the symptomatology of children with repaired esophageal atresia and distal fistula [35], but the absence of TM in esophageal atresia without fistula contradicts this.

Symptomatology

Classically, the signs and symptoms of TM have been described as occurring not at birth but instead appearing insidiously during the first weeks or months after birth [32, 36, 37]. However this standard has been challenged in a recent study that noted signs and symptoms in 95 % of the cases of congenital TM at birth [20]. Patients with esophageal atresia with distal fistula have a noisy barking expiration, especially during crying, but sometimes even at rest [26]. Often there is wheezing. If the TM has an extrathoracic component, there may be inspiratory stridor as well. Feeding usually exaggerates symptoms. Often the child feels uncomfortable during feeding. As a result the child wants to cry, thereby increasing the intrathoracic pressure but at the same time compressing the intrathoracic trachea even further. The child wants to exhale but cannot. Clinically there is opisthotonus.

Intercostal and substernal retractions occur and there is nose flaring. The child becomes cyanotic, and when hypoxia has taken effect, the child relaxes and may start breathing again. During such a life-threatening episode, the child may aspirate. Primary gastroesophageal reflux with or without aspiration has also be held responsible for these events [38], and it remains difficult to be certain about the primary causative factor: gastroesophageal reflux or TM [31].

A severity rating score for TM has been proposed [15]:

Mild TM
: Children have respiratory difficulties associated with infectious processes such as croup or bronchitis. These children have often problems with retained secretions.

Moderate TM
: Children present with classic symptoms such as stridor, wheezing, recurrent respiratory infections, and even cyanosis with exacerbations.

Severe TM
: Children present with stridor during tidal breathing, marked sputum retention, upper airway obstruction, reflex apnea, and even cardiac arrest.

Diagnosis

Awareness of the possibility of TM and knowledge of its symptomatology are of course important. This applies especially for the idiopathic form. In a group of 96 outpatients with idiopathic TM, mean age at diagnosis was 5.2 years (range 0–16 years) [23]. Moreover TM was not suspected before bronchoscopy in half of the patients with idiopathic TM. While the association between esophageal atresia with distal fistula and TM is well known among pediatric surgeons, attributing the actual symptoms to TM and proper management is more of a problem as symptoms in patients with repaired esophageal atresia with distal fistula may also be caused by gastroesophageal reflux or recurrent fistula.

Many methods have been used to diagnose TM through the years.

Plain X rays have a low sensitivity [39]. CT scanning is gaining popularity. It has a high sensitivity, it allows for 3D reconstruction, and it is fast and does not require general anesthesia. The disadvantage is radiation exposure, but dose reduction schemes are being developed [19, 40]. MRI is the preferred method for evaluating external compression [25, 41, 42]. General anesthesia has, however, to be given, which is not without danger [43]. The use of imaging techniques will undoubtedly increase as technology evolves. They certainly will allow in the future for a dynamic evaluation of the trachea in small children despite their “uncooperativeness.”

At present, endoscopy of the airway still plays a crucial role in the diagnosis [6]. First of all it allows for the diagnosis of concomitant anomalies

of the upper airway such as tracheal stenosis [44]. For observing the dynamics of the TM, general anesthesia in spontaneously breathing infants is required. Nowadays flexible endoscopes are often used. A tracheal collapse of more than 50 % during expiration or coughing or a ratio of the cartilage to the membranous tracheal wall of more than 3:1 is considered diagnostic [15, 23]. Bronchoscopy is, however, an invasive procedure. It requires general anesthesia, but spontaneous breathing. Kamata et al. selected those patients for surgery in whom there was a 70 % collapse of the airway during mechanical ventilation without spontaneous breathing [45]. In three of the six patients with tracheobronchomalacia, a pexy of the pulmonary artery was added to the aortopexy and one of the patients with pure bronchomalacia had just a pulmonary artery pexy.

Aortic arch anomalies can be diagnosed antenatally [46]. Not all cases in this publication were symptomatic at birth: of the five cases with double aortic arch, one fetus was aborted, one was asymptomatic, and the remaining three underwent surgery; of the six cases with right aortic artery and aberrant left subclavian artery, five remained asymptomatic and one underwent surgery, and finally of the eight cases with left aortic artery and aberrant right subclavian artery, one fetus was aborted while the remaining seven cases remained asymptomatic.

Treatment

It has been stated over and over again that TM improves with time [6, 31] and that medical treatment suffices in the meantime in most cases. It should be realized however that TM does not only just cause obstruction of the intrathoracic trachea during expiration. Sputum retention due to impaired secretion clearance and ineffective cough may lead to tracheal mucosal metaplasia, reduced cilia, atelectasis, and/or recurrent pneumonia [15, 31, 32, 47].

There is general agreement that severe TM needs urgent treatment [6, 26, 48]. In one series of TM associated with esophageal atresia and distal fistula, indications for surgery were episodes of apnea and cyanosis 65 %, recurrent pneumonia 25 %, and worsening stridor 46 % [49]. When TM is associated with tracheal stenosis or anomalies of the great vessels such as a pulmonary sling, these anomalies have their own treatment plans with concomitant or later aortopexy [19, 50–55]. After double aortic arch correction, symptoms may persist in up to 30 % of the cases [56].

For TM itself, several treatment options are available [6], but there is an absence of evidence to support any of the therapies currently used for the management of primary tracheomalacia [57].

Treatment Options

Tracheostomy and Long-Term Ventilation

These techniques have been the mainstay of therapy for severe TM for many years. Tracheostomy causes, however, additional tracheal injury. In the 1990s the percentage of infants and children requiring tracheostomy for TM varied widely from 12 to 62 % [6].

Continuous Positive Airway Pressure (CPAP)

CPAP with or without tracheostomy is an effective treatment for moderate to severe TM [58]. The disadvantage of CPAP is that it usually requires a long treatment period and hospitalization. Moreover it is associated with a delay in the commencement of oral feedings, retardation of speech and language, and potential developmental delay [22, 59]. CPAP can be considered as an initial treatment [6].

Fundoplication

The association between TM and gastroesophageal reflux has been recognized for a long time. Especially in severe TM associated with esophageal

atresia, one has argued about the primary approach: fundoplication or aortopexy. In a series of 22 infants presenting with severe respiratory symptoms after esophageal atresia repair, 13 (59%) had an initial TM procedure, stent, or aortopexy [38]. Respiratory symptoms improved in seven. Six of the seven got a fundoplication and all six improved. Nine (41%) had an initial fundoplication with improvement of symptoms in six. The non improving patients had an aortopexy later on, with improvement in all. The authors do not choose between both approaches as a first. In contrast Corbally et al. choose aortopexy as a first [49], which seems reasonable, but no time should be lost embarking on a fundoplication when the aortopexy is not effective.

Splinting of the Trachea

There have been several attempts at external splinting of the trachea and bronchi, e.g., with pericardial patches [60], silastic-impregnated Marlex mesh [61, 62], and costal cartilage [63]. Even ceramic rings have been advocated at least in adults [64]. External splinting techniques have not gained popularity because of the magnitude of the operation, especially when a long segment is affected. There is also concern regarding the growth of the trachea, when these techniques would be used in children.

Stenting of the Trachea

Stents in children were used for the first time in 1995 [65]. Today a wide variety of stents have become available. There are mainly three different types: metal stents, silicone stents, and biodegradable stents [66, 67]. Stents have the advantage of immediate relief of the problem, but stent displacement, formation of granulation tissue, and difficulties in removal at least when metal stents are inserted have limited their use. Biodegradable stents seem to be the future, but clinical trials have not been conducted so far due to the very low incidence of very severe TM. Today stenting is regarded as an option when other treatment modalities have failed [19, 66, 67].

Slide Tracheoplasty

Removal of the affected trachea with slide tracheoplasty has been described in an infant with congenital tracheal stenosis and TM after esophageal atresia with distal fistula repair.

Aortopexy

Aortopexy has been carried out through several approaches. Gross used a left anterolateral approach; Filler et al. used a right posterolateral approach in their first case, but shifted to a left anterior thoracotomy in the third intercostal space in the cases to come [4]. Gross removed part of the thymus and sutured the adventitia of the innominate artery to the posterior periosteum of the sternum with fine silk sutures. A detailed description of the technique was published in 1982 by the Toronto group [5]. In two cases a retropleural approach was used. The left lobe of the thymus was removed and the aortic arch and branches were exposed. The plane between the aorta and trachea was left undisturbed so that the anterior tracheal wall would follow the aortic arch when sutured to the sternum. Three to four nonabsorbable sutures were placed through the adventitia and a portion of the media of the following vessels: (1) aortic arch, at the level of the lateral border of the innominate artery; (2) anterior wall of the innominate artery, 0.5–1 cm from its origin; (3) aortic arch, at the level of the medial border of the innominate artery; and (4) aortic arch, 0.5 cm medial to the previous suture. The anterior sternum was dissected free and the ends of the sutures passed through the sternum and tied. Relief of the anterior compression of the trachea was evaluated either perioperatively or at the completion of the procedure. Spitz described in 1986 the use of a Dacron patch in order to distribute the traction on the aortic arch over a larger area [68]. Aortopexy through an anterior right thoracotomy has been performed as well [69]. Vaishnav and MacKinnon proposed a cervical approach with split of the upper sternum [70]. Brawn and Huddart advocated aortopexy

through a median sternotomy, claiming better access [71]. Bullard et al. entered the chest through a mediastinal window by resecting the costal cartilages II and III on the left [72]. When the distance between the aortic arch and the sternum is too long, a pericardial flap can be used to decrease the distance [73]. Some authors use pledge-supported sutures [74].

All approaches mentioned so far were performed through a thoracotomy. Thoracoscopic aortopexy was reported for the first time by DeCou et al. in 2001 [75]. Since then several reports of thoracoscopic aortopexy have been published [76–80]. Schaarschmidt did one aortopexy from the right in a patient who had a previous aortopexy through a left-sided thoracotomy [79]. Kane used a right thoracoscopic approach primarily [81].

Technique of Thoracoscopic Aortopexy [82]

Tracheal intubation and ventilation in combination with CO_2 insufflation are used. The child is placed in supine position close to the left edge of a short table (Fig. 49.1a). The left chest is 15° elevated, and the table is put in 15° reverse Trendelenburg. The left arm is abducted along the head so that the left axilla is free. The child's head is positioned in such a way that an intraoperative tracheoscopy can be performed. The midsternal line is marked for future suture insertion (Fig. 49.1b).

The surgeon stands at the left side of the table with the cameraperson below him and the scrub nurse at the lower end of the table (Fig. 49.2). The key screen is placed in front of the surgeon at the right side of the table, next to the patient's head. When intraoperative tracheoscopy is planned, the display of the tracheoscopy should be visible by the surgeon.

Three cannulae are inserted (Fig. 49.3). The first one is a 3.8 or 6 mm one for a 3.3 or 5 mm 30° telescope. In children below 2 kg, the smaller telescope is used. The first cannula is inserted in the midaxillary line at the level of the nipple. After confirmation that the first cannula is in the thoracic cavity, CO_2 pneumothorax is started. A pressure of 5–8 mmHg and a flow of 0.1–0.5 L/min usually suffice. There may be initial desaturation, which is counteracted by releasing the CO_2 pneumothorax, and adjustment of the ventilator setting (higher frequency but lower tidal volume). Two 3.5 mm cannulae for 3 mm instruments are inserted in triangle configuration with the telescope cannula, one lower down but more anteriorly and one higher up in the axilla. All cannulae should have snugly fitting sleeves for fixation to the thoracic wall. Fixating sutures should not only include the skin but also the underlying thoracic wall.

A magnificent view of the upper anterior mediastinum is obtained (Fig. 49.4a). Care is taken not to injure the left phrenic nerve, which lies in front of the left pulmonary pedicle. The mediastinal pleura is opened longitudinally over the thymus and the thymic gland is mobilized anteriorly and posteriorly. After complete anterior and posterior mobilization, the gland can be pushed to the right, but removal of the left portion makes the procedure easier. The aortic root with pericardial reflection, aortic arch, and innominate artery are freed but the adventitia is left intact (Fig. 49.4b). The area to be suspended is rather the ascending aorta and innominate artery and then the arch itself. When the distance between the aorta and back wall of the sternum is too large, then a pericardial patch with its base at the pericardial reflection on the aortic root can be constructed, but in small children the pericardium easily tears.

Sutures are placed transsternally in and out through the same 2–3 mm transverse skin incisions but through slightly different tracks through the sternum in order to create a bridge for the sutures (Fig. 49.4c). The best position for the sutures is a position directly in front of the vessels to be suspended. For identification of the best place, a needle is inserted through the skin and sternum in the upper midline. When the needle is in good position, a small incision is made. For transsternal suturing a rather large needle is needed. We have used Ethibond® 3/0 on a FS-1 needle, but others have used other materials and brands including Prolene® [75], Ticron® [48],

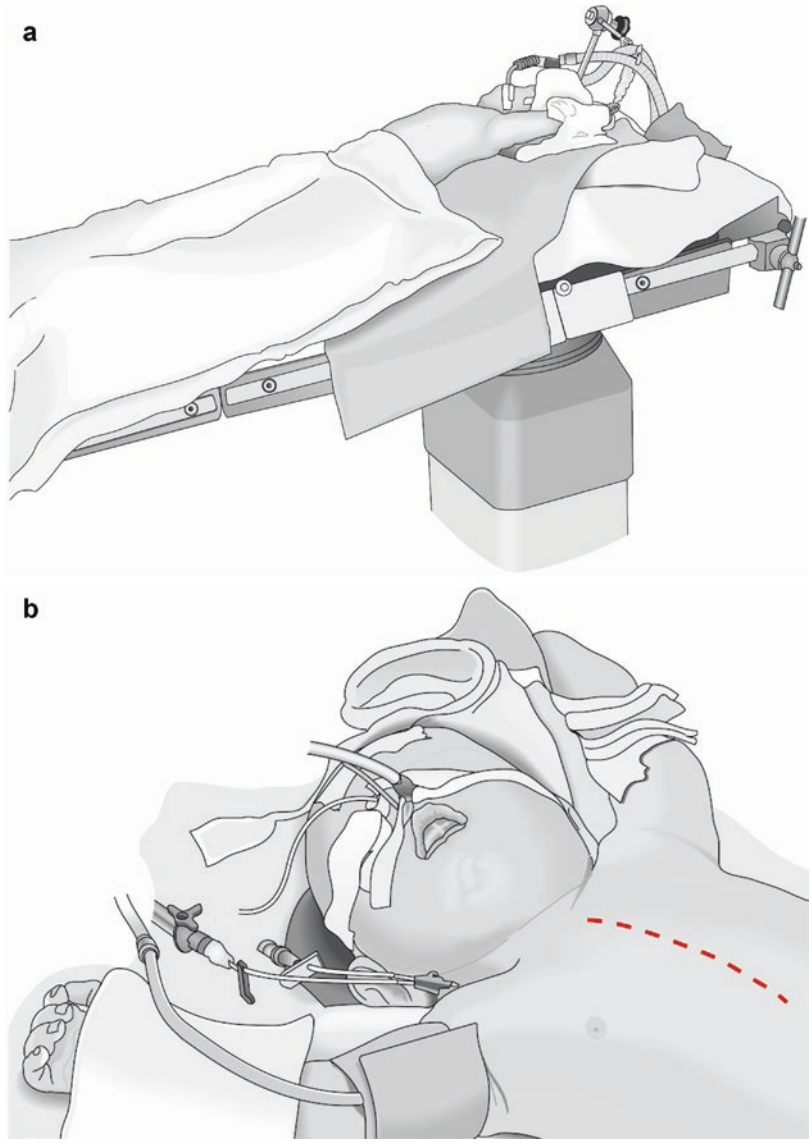


Fig. 49.1 (**a**) The child is placed in supine position close to the left edge of a short operating table (Reprinted with permission Bax and van der Zee [82]). The left chest is 15° elevated, and the table is put in 15° reverse Trendelenburg. The left arm is abducted along the head so that the left axilla is free. The child's head is put in such a way that an intraoperative tracheoscopy can be performed. (**b**) The mid-sternal line is marked for future suture insertion (Reprinted with permission Bax and van der Zee [82])

and silk [81]. The disadvantage of a large needle is its reduced maneuverability especially when the needle has been straightened. Moreover straightening of needles interferes with their design. For getting the needle out, a large-bore intravenous needle is passed transsternally through the same skin incision, but slightly more medial or lateral to the entrance of the suture so that a small bridge of sternum is between entrance and exit. The intrathoracic needle of the suture is then pushed into the intravenous needle and both are taken out en block (Fig. 49.4d). Getting a good bite of the adventitia of the aorta and innominate artery without taking the whole wall

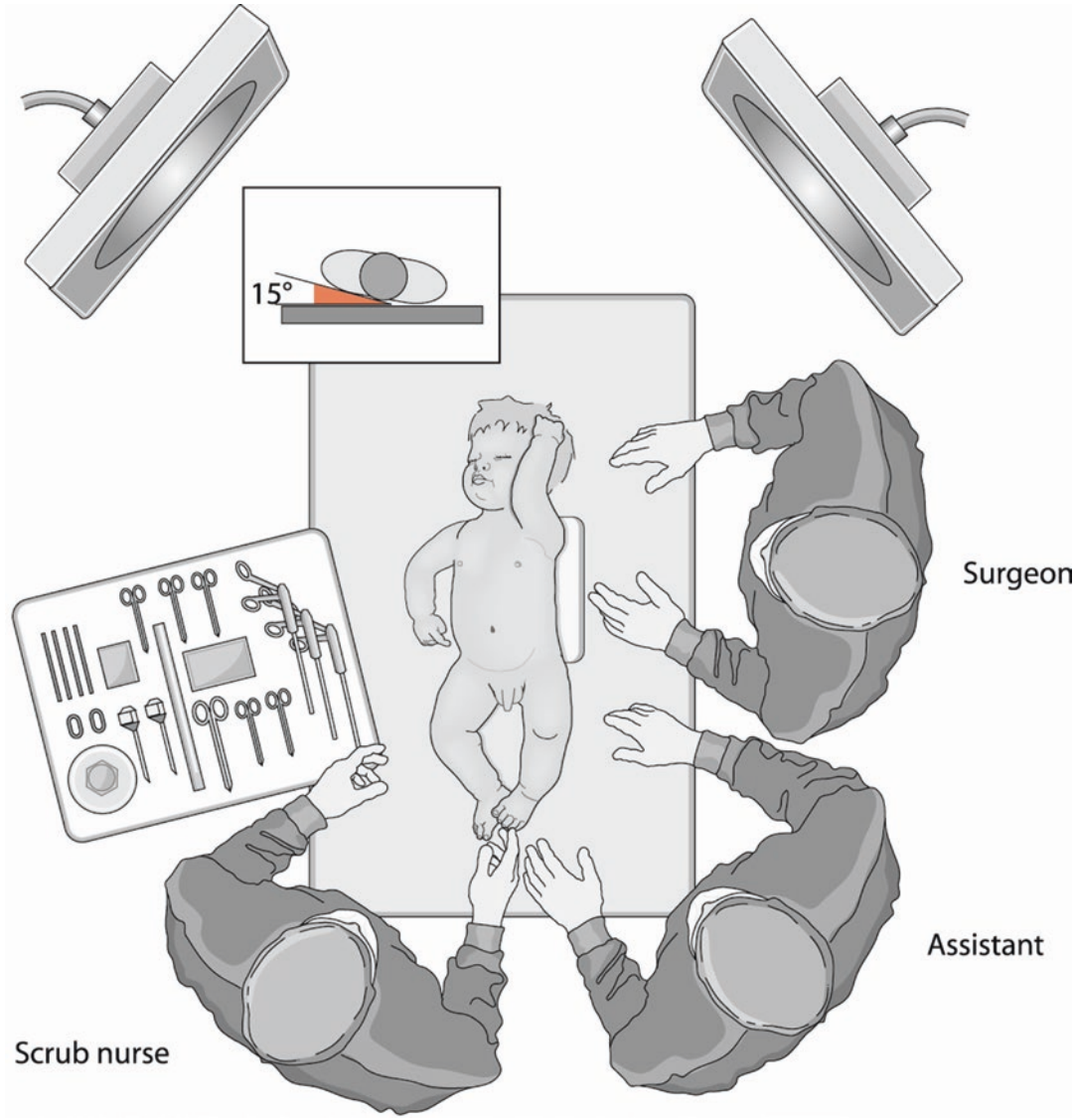


Fig. 49.2 The surgeon stands at the left side of the table with the cameraperson below him and the scrub nurse at the lower end of the table. The key screen is placed in front of the surgeon at the right side of the table, next to the patient's head (Reprinted with permission Bax and van der Zee [82])

is not simple, especially not with a large needle. Sutures with smaller needles can be used but these sutures should then be inserted through either a cannula or directly through the thoracic wall. The ends of these have then to be picked up transsternally with the use of nylon loops introduced through large-bore intravenous needles (Fig. 49.4e). At least three sutures should be placed, the first one at the pericardial reflection, a second one halfway the ascending aorta, and a third one at the takeoff of the innominate artery (Fig. 49.4c).

Perioperative tracheo-bronchoscopy has been advocated over and over again during the tying of the sutures, but TM is a dynamic event and spontaneous breathing is said to be important for evaluating TM. During aortopexy, however, children do not breathe spontaneously. Moreover the

child's position on the table during aortopexy is not ideal for a tracheo-bronchoscopy. Lastly, not much more than three of four sutures can be placed anyway. Dave and Currie, who published a series of 27 open and one thoracoscopic aortopexy, also have given up perioperative bronchoscopy [48]. During the tying of the sutures, care should be taken that the suspended vessels and especially the innominate artery do not kink. Pulse oxymetry of the right hand is helpful in this perspective. Pressing on the sternum during the tying of the sutures is advantageous as it decreases the distance between the sternum and the vessels to be suspended, thereby decreasing the likelihood of tearing out of the sutures.

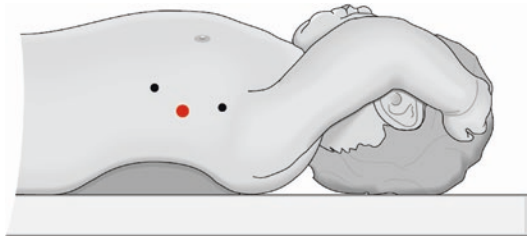
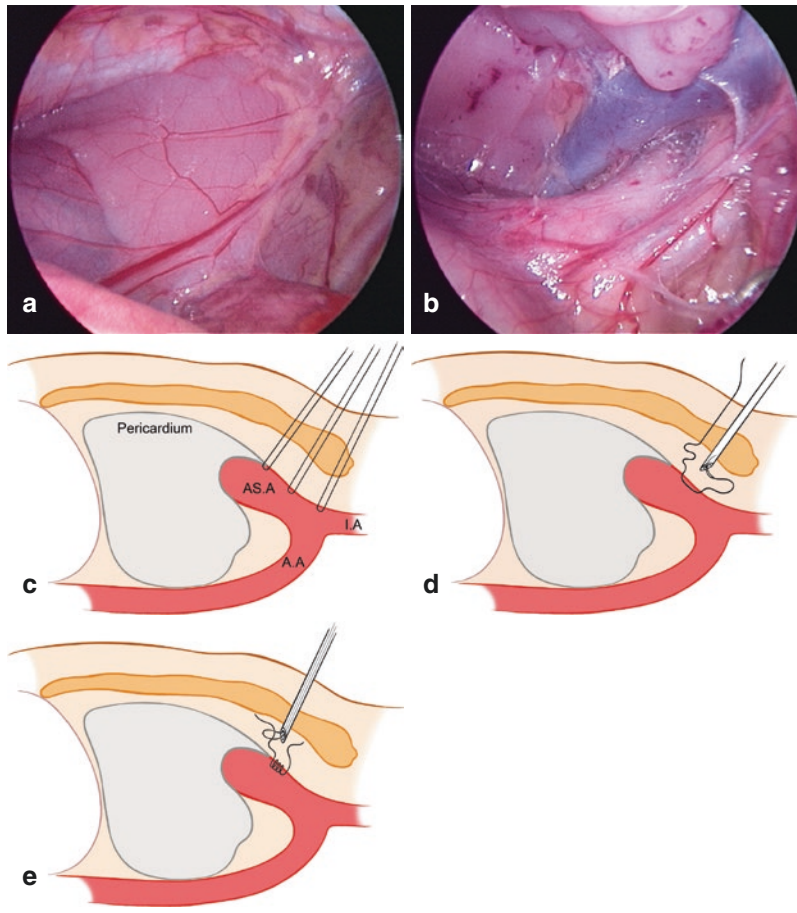


Fig. 49.3 Three cannulae are inserted. The first one is a 3.8 or 6 mm one for a 3.3 or 5 mm 30° telescope. In children below 2 kg, the smaller telescope is used. The first cannula is inserted in the midaxillary line at the level of the nipple. Two 3.5 mm cannulae for 3 mm instruments are inserted in *triangle* configuration with the telescope cannula, one lower down but more anteriorly and one higher up in the axilla (Reprinted with permission Bax and van der Zee [82])

At the end of the procedure, thymic tissue is removed when a partial resection has been undertaken. This can be done in a piecemeal fashion under vision with a mosquito inserted through one of the port sites. CO_2 pneumothorax is released, the lungs are expanded, and the skin incisions are closed with adhesive strips. A drain is not required when the procedure was smooth and lung trauma was avoided. Scars are minimal (Fig. 49.5).



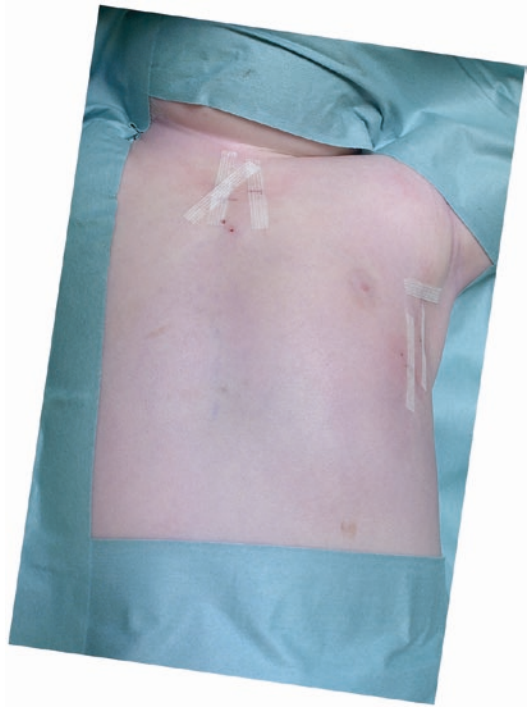


Fig. 49.5 The procedure results in minimal scars

Complications of Aortopexy

Massive hemorrhage due to tearing out of sutures that were inserted through the whole vessel wall has been described [71]. This can be avoided by meticulous placement of the sutures. Only bites of adventitia should be taken. It is stated that also part of the media should be included but this increases the likelihood of transarterial wall suturing. Phrenic nerve injury either transient or requiring plication of the diaphragm has been described [48, 74]. Postpericardiotomy syndrome and chylopericardium after aortopexy with pericardiotomy have also been described [83]. All these complications have been described after open aortopexy, but there is no reason why these could not happen after a thoracoscopic approach. Wound-related complications such as dehiscence have described after an open approach [74]. It is unlikely that these will occur when using a thoracoscopic approach.

Early Results of Aortopexy

When aortopexy is effective, detubation can be performed at the end of the procedure on the operating table or within a few days. The effectiveness of the procedure depends not only on the quality of the operation but also on whether the TM is idiopathic or not. In a series of 17 patients with idiopathic TM, aortopexy failed to relieve the symptoms in 10 of them (59 %) [31]. In contrast the same institution reported an 86 % improvement after aortopexy in series of patients with esophageal atresia [84]. In their series of 28 children with TM, 15 in association with esophageal atresia and 13 idiopathic, 26 responded well to aortopexy [48]. In TM in combination with esophageal atresia the success rate was 100 %; in idiopathic TM the success rate was 86 %. Recurrent chest infections and asthma-like symptoms however occurred in 25 % of the patients. In a series of 20 patients with TM, including five after esophageal atresia repair and two with double aortic arch, good long-term results with a mean follow-up of 7.8 years were obtained in 80 % of the cases [69].

Not many results after thoracoscopic aortopexy have been described. Van der Zee and Bax reported good results in four of six patients [80].

Fig. 49.4 (**a**) A magnificent view of the upper anterior mediastinum is obtained. The thymic triangle with sternum in front, phrenic nerve posteriorly, and pericardium distally is identified. The mediastinal pleura is incised over the thymus and the left thymic lobe is mobilized, pushed to the right or even better removed. (**b**) The ascending aorta with overlying pericardial reflexion and the innominate artery are identified. The adventitia is left intact. (**c**) Three nonabsorbable sutures are passed through small skin incisions through the sternum. The adventitia is taken in the sutures and the needles are passed back through the sternum parallel to the entrance passage and out through the entrance skin incisions. (**d**) Getting the suture needle out again is facilitated by passing a large-bore intravenous needle through the sternum parallel to the entrance trajectory and the suture needle is inserted into the tip of the intravenous needle. Both needles are then taken out en block. (**e**) Hitching the adventitia well, a smaller suture can be used. The ends of the suture can be taken out separately through the sternum using nylon loops inserted through large-bore intravenous needles

In two patients life-threatening events recurred after 2 and 4 weeks. Both patients had a repeat thoracoscopic aortopexy and did well afterward. Perger et al. reported about five patients, four of them having TM in association with esophageal atresia [78]. Two of them had a pneumothorax postoperatively. Symptoms resolved in all, but three out of the five kept on having respiratory infections.

Longer Term Results of Aortopexy

The contribution of aortopexy in the long-term results is difficult to determine as idiopathic TM and TM associated with esophageal atresia have a tendency to improve with time.

Conclusions

A higher awareness of TM will undoubtedly increase the diagnostic incidence of TM, especially of the milder forms. Tracheobronchoscopy remains an important diagnostic modality both for assessment of tracheal collapsibility during spontaneous breathing and for diagnosing associated anomalies of the tracheobronchial tree. High-quality imaging techniques like multidetector CT and MRI have become available. However general anesthesia is required for MRI and a CT scan exposes the child to radiation. Whether the use of such techniques is justified depends on the severity of TM.

There is no discussion that severe TM, and especially TM resulting in life-threatening events, should be treated aggressively. Thoracoscopic aortopexy is an excellent first treatment option. When it fails to resolve the symptoms, a laparoscopic fundoplication may be additionally needed. As thoracoscopic aortopexy is a much less invasive procedure than aortopexy through thoracotomy, its indications could be extended to moderate or even less severe forms of TM. Aortopexy, whether open or thoracoscopically, is not a panacea for all patients with TM. Stenting is an alternative, but not as a first treatment option.

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Part X

Further Out from EA Repair: Functional Results and the Quality of Life

50 Long-Term Results: Prognosis, Developmental Milestones, and Quality of Life After Surgery for Esophageal Atresia

Daniel C. Aronson

Short-Term, Midterm, and Long-Term Prognosis

Over the last 70 years, the survival of patients with esophageal atresia has increased from 0 % to around 95 %. Today, mortality is largely determined by associated comorbidities, mostly the cardiac anomalies. The notion that a patient, who is discharged from hospital after successful reconstruction of an esophageal atresia, is definitely "cured" has been abandoned. Instead patients may be facing many long-term problems like feeding disturbances related to recurrent anastomotic stenosis, gastroesophageal reflux, and motility disorders. Additionally, respiratory problems, either caused by concomitant tracheomalacia or by gastroesophageal reflux with recurrent aspiration, are some of the important problems that mandate regular follow-up.

Respiratory problems in the first year of life may be caused by recurrent fistulas, gastroesophageal reflux, tracheomalacia, or associated anomalies such as laryngotracheoesophageal cleft. These must be promptly recognized and treated to prevent serious morbidity. For further information, we refer to previous chapters. Late mortality may be related to associate anomalies or may occur from late complications of the esophageal anomaly itself or of its treatment [1]. Even infants with a smooth initial course may eventually suffer sudden death related to tracheomalacia, gastroesophageal reflux, or food impaction in the esophagus [1, 2]. In many cases, respiratory problems tend to improve later in life, but up to 40 % of adults retain the typical barking cough of tracheomalacia and about 25–40 % continue to have respiratory problems such as recurrent wheeze, asthma, bronchitis, and pneumonia [3–5].

There has been much interest in late morbidity, which can be related to the esophageal anastomosis, to abnormal esophageal motility, to gastroesophageal reflux, and to respiratory problems [6–9]. Disturbed esophageal motility and concomitant gastroesophageal reflux have been the most troublesome problems, since this may cause strictures at the anastomotic site or at the lower esophageal sphincter. Abnormal esophageal motility contributes to long-term dysphagia in almost one third of the adult patients. This symptom is probably inadequately recognized, as some individuals are so adapted to their motility problem that they do not consider it to be abnormal [5]. A relationship between gastroesophageal reflux and Barrett's esophagus (intestinal metaplasia), esophageal adenocarcinoma, or squamous cell carcinoma has been reported [6, 7, 10, 11, 12]. However, the few described cases do not

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unequivocally establish a relationship between esophageal atresia and the development of esophageal cancer.

Several studies have shown that gastroesophageal reflux and esophagitis persist in a significant number of adolescents and adults [5–8]. Since reflux and esophagitis may be obscure in patients with EA, the necessity for and the timing of a surveillance esophagoscopy have been under debate, especially in view of the potential development of Barrett's esophagus and esophageal cancer. Interval esophagoscopy has been recommended every 3–5 years [8]. However, not only the efficacy of screening but also its cost-effectiveness and the psychological aspects of implementation of a screening program must be taken into consideration, including subjecting (ex)-patients with minor or no complaints to invasive procedures under anesthesia [5].

Long-term growth and development have been reported to be within normal limits in most follow-up evaluations. A large proportion of patients are below the fifth percentile at 6 months of age but show catchup growth in almost all cases within the first 5 years of life [13].

Developmental Milestones

The dramatic improvements in the treatment of various congenital anomalies like esophageal atresia but also other chronic and even life-threatening diseases over the last few decades have lead to an increased survival of pediatric patients. The price of this success is a growing population of adults with a chronic condition. As a consequence, physicians will increasingly be confronted with young adults who have grown up with a chronic disease due to a congenital malformation. This requires physicians with special interest and knowledge of the implications of chronic pediatric disease, who can manage the transition from pediatric to adult medical care.

Children are continually developing via interaction with their environment. As Piaget and others demonstrated, their cognitive development progresses through a systematic and predictable sequence [14]. These norms are established for age, physical growth, and adaptive, cognitive, and social capacities and form a standard pattern of growth and evolution in healthy subjects with a normal mental development. Next to these steps in maturing, the achievement of developmental milestones in adolescence, such as the search for contact outside the family, or acquisition of independence, is essential to the adaptation to adult life. This is usually referred to as the "course of life" [15]. The impact of chronic diseases in childhood on the course of life is not yet fully defined. A chronic disease increases the individual's dependence on caregivers, decreases participation in peer-based or school-based activities, and hinders the achievement of developmental milestones [15]. This delay can be tested with a validated instrument called the Course of Life Questionnaire, developed to assess the course of life of young adults with a chronic disease thereby allowing comparison with healthy peers [16]. Items in this questionnaire relate to behavioral characteristics of certain ages, developmental tasks, and limitations children face growing up with a chronic disease. Most questions interrogate, whether the responder had achieved certain milestones or at what age they were achieved. Items are divided into five scales: autonomy development, psychosexual development, social development, antisocial behavior, and substance use and gambling. The only study done so far compared the course of life of a reference group of 508 healthy young adults with a group of 650 young adults with a chronic disease, all aged 18–30 years. The latter group was composed of 348 survivors of childhood cancer, 93 with anorectal malformations, 72 with Hirschsprung's disease, 61 with esophageal atresia, and 76 with end-stage renal disease [15]. In contrast to the other chronic diseases tested, only the course of life in the individuals who had been treated for esophageal atresia appeared to be as favorable as that reported by the control group and no delays in the domains tested were recognized. While factors such as coping with the disease, family functioning, and social support were not separately taken into account, this finding was explained by the authors by the fact that esophageal atresia is treated so early in life that it is not

experienced as a life-threatening disease. Affected individuals are therefore able to adjust to their condition and to participate normally in social activities. The authors of this study warn the reader that the course of life is measured in a retrospective manner, which limits the range of topics highlighted. In order to prevent bias due to inadequate memory, questions were factual and did not go further back to primary school.

Another study showed that most of the 119 adult individuals (16–48 years of age) with a reconstructed esophageal atresia were leading a normal life in regard to work or education. They were either employed and had finished high school (77 %) or were still in school full time (31 %) [5].

Quality of Life

The ultimate goal of treatment has moved from mere survival to alleviating symptoms and to improving quality of life. In the last decade, several study groups have therefore developed an interest in the influence of esophageal atresia and its long-term sequelae on the quality of life of surviving patients. Although before this époque several older studies mention quality of life after correction of esophageal atresia, most of these studies focus on the number of medical problems and on psychological development and not on quality of life per se [17–21].

Quality of life is studied by the use of standardized and validated quality of life questionnaires, comparing the quality of life of a certain patient group with healthy controls. Although definitions of quality of life vary widely, there is consensus about two central aspects. Firstly, quality of life should be assessed from the patient's perspective whenever possible. Secondly, quality of life should be regarded as a multidimensional construct incorporating at least three broad domains that can be affected by one's disease or treatment, including physical, mental, and social functioning [22, 23]. Most instruments in quality of life research can be classified as either generic or disease specific. The generic instruments are designed to measure all aspects of health and well-being regardless of the underlying disease and enable comparisons across different disease groups and with healthy reference groups. However, the generic instruments are limited as they do not measure aspects that are of particular relevance to specific disease groups, such as disease symptoms. Conversely, disease-specific measures examine the symptoms of specific disease groups and how they function. Various questionnaires are available to measure the generic or the disease-specific quality of life, and a choice is made by the study group, usually depending on the aim of the study and the age restrictions of the questionnaire [24]. Ideally, generic and disease-specific questionnaires are selected, and often, questionnaires that measure psychosocial functioning are added.

An example of a QoL questionnaire for adults is the 36-item Short Form Health Survey (SF-36), a widely used generic, validated questionnaire for health-related quality of life [25]. It contains scales of vitality, social functioning, emotional role functioning, and emotional well-being that make up the summary measure of mental health. Furthermore scales of physical functioning, physical role functioning, bodily pain, and general health perceptions make up the summary measure of physical health. Positive affect, an extra dimension of mental quality of life, can separately be measured by a Positive Affect Scale (PAS) [26, 27]. Examples of QoL questionnaires for children are the Child Health Questionnaire Child Form (CHQ-CF87) for children ≥10 years of age and the Child Health Questionnaire Parent Form (CHQ-PF50) for parents of children ≤13 years. These instruments use item scales for physical functioning, role functioning/emotional behavior, role function physical, bodily pain, general behavior, mental health, self-esteem, general health perceptions, family activities, family cohesion, and parental impact [28–30].

Examples of disease-specific quality of life instruments to assess symptoms and psychosocial functioning directly related to EA are Gastrointestinal Quality of Life Index (GIQLI) and the Respiratory Symptoms-Related Quality of Life Index (RSRQLI). The GIQLI is a 36-item questionnaire concerning four domains; physical

well-being, gastrointestinal symptoms, social well-being, and emotional well-being. Scores below a certain cutoff point indicate ongoing GI symptoms that can be further assessed by creating specific subdivisions for gastroesophageal reflux, functional gastrointestinal disorders, bowel function, etc. [31].

The RSRQLI has been developed by the pulmonologists and pediatric surgeons of the University of Helsinki [32]. The instrument was designed to measure the quality of life related to respiratory diseases through a 15-item questionnaire.

Many questionnaires measuring psychosocial functioning are available. To name a few that have been used in the literature reviewed, the Illness Cognition Questionnaire (ICQ) was developed to assess illness cognitions that reflect different ways of evaluating the inherently aversive character of a chronic condition [33]. It contains three scales, helplessness, acceptance, and disease benefits and as a supplement asks for the positive and negative influences of various aspects of disease on life [5, 33].

Self-esteem can be separately measured by the use of the Self-Perception Profile for Children (SPPC) which is a 36-item questionnaire designed for 8–12-year-olds [17]. Also instruments are available for the use of parents, such as the Child Behavior Checklist (CBCL) which tests behavioral and emotional problems of the child [34]. The Family Assessment Device (FAD) measures family functioning, and the Life Events Questionnaire (LEQ) has proved to be a reliable indicator of familial psychosocial stress [17, 35, 36]. The Rosenberg Self-Esteem Scale (RSES), the Beck Depression Index (BDI), and the Cohen's Test for Life Management Ability (CTLMA) have all been used in an attempt to define the negative impact of chronic diseases in childhood [32, 37].

To date, only six studies that have used standardized and validated quality of life questionnaires to study esophageal atresia patients are available. Unfortunately, the choice of questionnaire itself is far from standardized, which makes the comparison of the various studies complicated. In one of these studies, the quality of life for long-gap esophageal atresia patients is examined together with the functional results from eight patients after colon interposition [20]. Another study, from the same research group, examined the quality of life in 58 patients more than 20 years after correction of esophageal atresia [21]. These results showed "acceptable" quality of life after colon interposition and "excellent" quality of life after primary repair of esophageal atresia. A third study addressed the quality of life as medium-term outcome after primary and secondary gastric transposition for esophageal atresia in 28 patients with a mean age of 13 years [38]. Quality of life could not be completely compared to the quality of life of healthy individuals, since the GIQLI questionnaire had been modified to include more esophageal-specific items and exclude items inappropriate for the specific age groups tested. However, the mean scores of the individuals after primary gastric transposition remained within the 95 % confidence interval (CI) as compared to healthy individuals but were outside the 95 % CI after secondary gastric transposition [38]. The parental reports showed that children in both groups experienced difficulties in all aspects of eating, which affected their quality of life adversely. Patients after secondary gastric transposition experienced more disease-specific symptoms [38]. Koivusalo et al. [32] reported that the generic quality of life in most of the adults after esophageal atresia repair was no worse than that of the general population, but individuals with low health-related quality of life scores in the generic SF-36 questionnaires scored low in the disease-specific questionnaires (GIQLI and RSRQLI). GIQLI dimensions measuring gastroesophageal reflux were lower after esophageal atresia repair. Overall, in 15 % of patients, morbidity from esophageal functional disorders and/or respiratory disorders impaired health-related quality of life. Quality of life did not differ between different types of esophageal atresia or between the different types of esophageal reconstruction [32]. The study of Deurloo et al. [39] compared the generic quality of life after correction of esophageal atresia in a group of 16–48-year-olds with that of healthy controls and

found no differences in the overall physical and mental health. General health was reported to be worse in the 25 % of individuals that had persistent gastrointestinal complaints, e.g., dysphagia. Only 8 % of the patients indicated that they felt limited because of their reconstructed esophageal atresia. This subgroup of patients felt their quality of life to be significantly impaired in several dimensions. Overall, however, individuals at long-term follow-up after esophageal atresia correction perceived their quality of life to be good, although scores on the domains of general health and vitality were lower than healthy controls. Surprisingly, the presence of other congenital anomalies did not seem to influence the quality of life in this study group [39].

One study addressed the health-related quality of life in children and/or adolescents after reconstructed esophageal atresia among 37 patients aged 6–18 years and 24 parents [29]. In the individuals tested, most domains of the health-related quality of life assessment were comparable to healthy controls. But both the patients and the parents scored significantly lower on the domain general health perception. Specifically gastro-esophageal reflux symptoms reduced general health perception, as did older age at follow-up and concomitant anomalies. According to the parents, the esophageal atresia patients experience negative consequences in their daily life such as gastrointestinal symptoms. Effect sizes of this domain indicate a moderate-to-large clinical effect. Scores in the family activities domain showed that children and adolescents reported that their health did not limit or interrupt family activities nor was it a source of family tension. In fact, it may have even strengthened the relationships between family members.

In summary, two aspects of these quality of life studies are of great importance. In the first place, parents of newborns with esophageal atresia can be reassured that their child has a good long-term outlook and should be able to lead a normal life with normal developmental milestones. Secondly, health-care workers and parents should be aware that esophageal atresia-related symptoms have a negative influence on the health-related quality of life. Careful follow-up focused on diagnosing and treating these symptoms vigorously may further improve the long-term outcome on the quality of life.

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Outcomes of Oesophageal Atresia Beyond Childhood: Helsinki Experience

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Saara J. Sistonen, Mikko P. Pakarinen, and Risto J. Rintala

Introduction

Survivors of oesophageal atresia are reaching their adulthood in large numbers for the first time thus allowing assessment of true long-term outcome among these patients. Patients with repaired oesophageal atresia have significant gastro-oesophageal [1–5], respiratory [1, 2, 5–7] and musculoskeletal problems beyond childhood [2].

In 2003, we initiated a cross-sectional population-based follow-up study to evaluate late outcomes in adult patients, who had undergone neonatal repair of oesophageal atresia. We aimed to study oesophageal function and morbidity, oesophageal metaplasia and cancer, respiratory morbidity, and clinical characteristics of musculoskeletal anomalies, especially spinal defects, at adult age.

Patients and Methods

The original study population consisted of 588 patients treated for oesophageal atresia in the Children's Hospital, University of Helsinki, from 1947 to 1985. A total of 235 alive patients with their native oesophagus were included. Of the 235 contacted patients, 169 (72 %) responded. The first 101 (median age 36 years), who replied and agreed to participate, underwent clinical investigations. The clinical and demographical characteristics of the study group were statistically similar to those of non-participants (Table 51.9). All patients responded to a symptom questionnaire including questions about oesophageal, respiratory, musculoskeletal symptoms and quality of life (SF-36, GIQLI, RSRQLI). Age- and sex-matched healthy controls ($n = 287$) filled identical questionnaires. The study patients underwent upper gastrointestinal endoscopy with biopsies, oesophageal manometry, pulmonary function tests and full orthopaedic evaluation with radiographs. The incidence of cancer among oesophageal atresia patients was evaluated from population-based countrywide cancer registry that covers practically 100 % of all cancer cases.

Results

Survival

The survival with oesophageal atresia has dramatically improved since the beginning of its successful surgical treatment, being nowadays well over 90 % in dedicated centres [8]. Today, even most infants with very low birth weight and severe cardiac malformations survive due to improvements in surgery and in modern intensive care.

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In the Children's Hospital, Helsinki University, Finland, mortality after oesophageal atresia repair has markedly decreased over the last decades (Table 51.1). In the early years, high mortality was associated with failure of surgical treatment, pneumonia, problems related to prematurity, and trisomies 18 and 21 with multiple anomalies. More recently, the main causes of death have been prematurity with low birth weight and trisomies 18 and 21 with major cardiac defects. Nowadays, nearly all patients will survive.

Table 51.1 Numbers of patients undergoing surgery for esophageal atresia and percentages discharged from hospital alive by year of operation in the Hospital for Children and Adolescents, Helsinki University, Finland, according to Louhimo [9] and our own work

Time-period	Number of patients	Survival (%)
1947–1956	100	19
1956–1960	100	43
1960–1965	101	56
1965–1971	101	70
1971–1978	100	85
1978–1985	86	85
1989–2007	89	97

Oesophageal Morbidity

Oesophageal atresia and its surgical repair disrupt the anatomy and innervation of the oesophagus, most likely contributing to oesophageal dysmotility. Oesophageal dysmotility predisposes to gastro-oesophageal reflux (GOR) and its complications. Significant GOR is a frequent finding after surgical repair of oesophageal atresia [2–5, 10–14], necessitating medical or surgical management in most children. Several recent endoscopic studies of adult oesophageal atresia patients have frequently demonstrated oesophagitis and intestinal metaplasia (Table 51.2), and even cases of oesophageal cancer (Table 51.3).

Oesophageal atresia is often associated with various oesophageal symptoms: regurgitation, heartburn, aspiration and dysphagia. Incidence of dysphagia ranges from 39 to 77 % and GOR from 17 to 63 % [2–5, 10–14, 22]. Most of these studies involved children and adolescents, but not adults. Typical late complications of the oesophageal anastomosis are oesophageal stricture in 30–56 % and recurrent tracheo-oesophageal fistula in 5–14 % [6, 7, 14, 23, 24]. Strictures are more common in patients with long-gap atresia

Table 51.2 Incidence of gastro-oesophageal reflux symptoms and histologically proven oesophagitis and Barrett's oesophagus in endoscopic long-term follow-up studies

References	Age (years) (mean)	GOR symptoms	Oesophagitis	Barrett's oesophagus
Biller et al. (1987) [1]	22–31 (26)	9/12 (75 %)	4/12 (33 %)	1/12 (8 %)
Krug et al. (1999) [3]	18–26 (22)	13/39 (33 %)	9/17 (53 %)	2/17 (12 %)
Deurloo et al. (2003) [4]	28–45 (34)	15/40 (38 %)	19/21 (90 %)	1/21 (5 %)
Deurloo et al. (2005) [15]	10–26 (17)	23/86 (27 %)	30/40 (75 %)	0/40 (0 %)
Taylor et al. (2007) [5]	20–48 (33)	63/83 (76 %)	36/62 (58 %)	7/62 (11 %)
Sistonen et al. (2010) [16]	22–56 (36)	34/101 (34 %)	25/101 (25 %)	6/101 (6 %)
Total	10–56	157/361 (~43 %)	123/253 (~49 %)	17/253 (~7 %)

Table 51.3 The six reported cases of oesophageal cancer after repair of oesophageal atresia

References	Age (years)	Gender	Histology
LaQuaglia et al. (1987) [17]	44	Female	Squamous cell carcinoma
Adzick et al. (1989) [18]	20	Female	Adenocarcinoma
Deurloo et al. (2001) [19]	38	Male	Squamous cell carcinoma
Pultrum et al. (2005) [20]	22	Female	Adenocarcinoma
Alfaro et al. (2005) [21]	46	Female	Adenocarcinoma
Taylor et al. (2007) [5]	44	Not reported	Squamous cell carcinoma

[6]. Persistent strictures are often associated with GOR [25] and thus require prompt antireflux treatment with fundoplication in addition to dilatations or stricture resection or both.

Oesophageal atresia is also associated with oesophageal dysmotility, low oesophageal distal wave amplitudes and non-propagating peristalsis of the oesophagus [10–12, 26]. Lack of distal oesophageal contractions correlates with the development of GOR [26], and patients reporting dysphagia often will have more disturbed motility and lower scores for quality of life [13].

In our population-based adult study, GOR occurred in 34 % and dysphagia in 85 % in patients post-oesophageal atresia repair versus 8 % and in 2 % in healthy controls ($p < 0.001$ for both). The endoscopic findings included hiatal hernia (28 %), Barrett's oesophagus (11 %), oesophagitis (8 %) and anastomotic stenosis (8 %). Three patients had an oesophageal diverticulum at the site of the anastomosis, and one recurrent tracheo-oesophageal fistula was found and treated successfully by bronchoscopy and laser. Histology showed oesophagitis in 25 % and epithelial metaplasia in 21 % (15 % gastric and 6 % intestinal metaplasia). All epithelial metaplasia were CDX2 positive, and those with intestinal metaplasia also demonstrated MUC2 positivity. Oesophageal metaplasia was associated with oesophagitis in 7 of the 21 patients. None of the patients had oesophageal dysplasia or carcinoma. The occurrence of pathological findings at endoscopy or histology had no correlation with symptoms of GOR or dysphagia. Patients with oesophageal columnar metaplasia had more anastomotic complications than do the rest of the patients (Table 51.4).

Oesophageal manometry demonstrated non-propagating peristalsis in most patients and ineffective distal oesophageal pressure in all. Manometrical abnormalities were significantly more common in those with epithelial metaplasia ($p < 0.02$) (Fig. 51.1).

Bars represent wave amplitudes of the oesophagus. The first column represents the minimum of normal values; the second, a median value for all patients; and the third, the value for patients with metaplasia. Normally, distal wave amplitudes grow stronger when moving from the proximal to the distal oesophagus. All adult patients with repaired oesophageal atresia had low distal wave

Table 51.4 Anastomotic complications

Complication	All ($n = 101$) N (%)	Metaplasia ($n = 21$) N (%)	p-value
Early stricture resection	4 (4)	3 (14)	0.06
Recurrent fistula	10 (10)	6 (29)	0.02
Late stricture	8 (8)	5 (24)	0.03
Long gap requiring myotomy	5 (5)	4 (19)	0.03

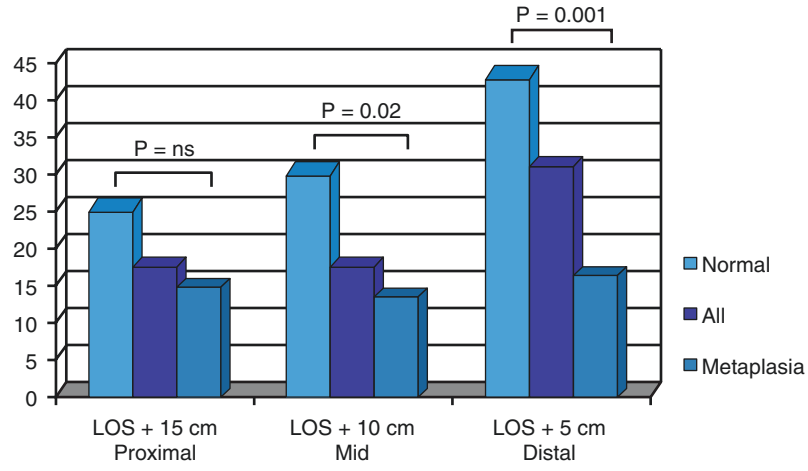


Fig. 51.1 Oesophageal distal wave amplitudes in the proximal, mid- and distal oesophagus

amplitudes, and patients with metaplasia even lower. In addition, none of the patients with epithelial metaplasia exhibited propagating peristalsis, and the difference between all patients and patients with metaplasia was significant ($p \leq 0.02$).

Anastomotic complications, age, low distal oesophageal pressure and defective peristalsis predicted development of epithelial oesophageal metaplasia (Table 51.5). Of the patients with epithelial metaplasia, 72 % were male, and 76 % were older than 30. The occurrence of epithelial metaplasia was associated with increasing age.

Cancer

Reports on oesophageal cancer among young adults with repaired oesophageal atresia (Table 51.3) arouse concern about risk for oesophageal cancer after repair of oesophageal atresia, and the necessity of long-term surveillance beyond childhood. Reflux oesophagitis and oesophageal columnar metaplasia are typical findings among oesophageal atresia patients and represent risk factors for oesophageal adenocarcinoma.

Despite high incidence of oesophageal metaplasia, none of the Finnish oesophageal atresia patients had oesophageal cancer. The number of person-years at risk was 8,034. Three patients had had cancer in other organ systems (SIR, 1.0; 95 % CI, 0.20–2.8); one had a lymphoma in the small intestine, one leukaemia and one uterine carcinoma. The overall cancer incidence was similar as in the general population. Our study showed that the statistical risk for oesophageal cancer after repair of oesophageal atresia was less than 500-fold than that of the general population.

Table 51.5 Multivariate logistic regression model for occurrence of oesophageal epithelial metaplasia

	OR (95%CI)	*p*-value
Early stricture resection	24.0 (2.3–260)	0.008
Recurrent fistula	24.0 (2.2–250)	0.009
Age >30 years	20.0 (1.3–310)	0.034
Long gap requiring myotomy	19.0 (2.0–180)	0.011
Late stricture	8.6 (1.7–45)	0.011
Distal wave amplitudes <25 mmHg	2.6 (0.68–10)	0.002
Non-propagating peristalsis	2.2 (0.43–11)	0.014

Respiratory Morbidity

Respiratory problems are also common in children and adolescents with oesophageal atresia and tracheo-oesophageal fistula [2, 6, 27, 28]. The occurrence of respiratory symptoms ranges from 33 % to 41 % [2, 5, 27–29]. Typical respiratory symptoms associated with oesophageal atresia include aspiration, failure to thrive, choking, wheezing, persistent cough, repeated respiratory infections and asthma [6, 27, 28, 30]. Wheeze occurs in approximately 37 % of the survivors of oesophageal atresia with no tendency to improve with age [8, 27, 29, 31]. Prevalence of doctor-diagnosed asthma during childhood and adolescence after repair of oesophageal atresia has been 12–29 % [5, 28–31]. Such a prevalence seems higher than in the general population of children (8.8 %) [28] and in adults (6 %) [32]. Approximately 10–20 % have severe tracheobronchomalacia with airway instability and collapse [8, 33]. Recurrent respiratory infections, persistent cough and wheeze are typical symptoms in childhood [27] and in adolescence [28], with a tendency to improve with age. However, repeated infections, aspiration and persistent tracheo-oesophageal fistula may result in irreversible lung damage with bronchiectasis and chronic pulmonary disease. Recurrent chest infections such as bronchitis and pneumonia occur in up to two-thirds of the survivors in the early years of life, but respiratory morbidity decreases in frequency and severity as the child reaches late adolescence [27].

In the few adult studies on oesophageal atresia patients, 33 % had respiratory symptoms [2, 5], and restriction was the main ventilatory defect [1, 2]. A strong connection exists between severity of GOR and persistence of respiratory symptoms among oesophageal atresia survivors. Although

such respiratory problems are common in children and adolescents, long-term outcomes beyond childhood have been unknown.

In our study, the patients had significantly more respiratory symptoms and infections as well as asthma and more often impaired respiratory symptom-related quality of life when compared to those of controls ($p \leq 0.002$) (Table 51.6). Among our adult oesophageal atresia patients, 11 % and 2 % of the controls had current respiratory symptoms ($p < 0.001$). Fifty-six percent and 70 % of the patients had a history of pneumonia and bronchitis (controls 20 % and 50 %, $p < 0.001$); 16 % of the patients and 6 % of the controls had doctor-diagnosed asthma ($p < 0.001$). Impaired respiratory-related quality of life was reported by 11 % of the patients but only in 6 % of the controls ($p < 0.001$).

Pulmonary function tests (Table 51.7) showed obstruction in 21 %, restriction in 21 % and both in 36 % of the patients. Only 20 % of the patients had normal pulmonary function. Bronchial hyperresponsivenes was detected in 41 % of the patients in histamine challenge test, and in 15 %, it was compatible with asthma. A total of 11 % had elevated exhaled nitric oxide levels indicating airway inflammation. Thoracotomy-induced rib fusions and surgical complications leading to GOR-associated oesophageal epithelial metaplasia were the most significant risk factors for restrictive ventilatory defect.

Of children and adolescents with repaired oesophageal atresia, restrictive pulmonary function occurs in 21–40 %, and obstructive PF in 12–54 % [28, 34–36]. The pulmonary function abnormalities did not correlate with current respiratory or oesophageal symptoms. The reason for pulmonary function abnormalities remains unclear, but it has been suggested that they were caused by permanent lung damage from recurrent aspiration in the patients' early years [2], by poor tracheal clearance leading to recurrent episodes of bronchitis or pneumonia leading to lung damage [30, 35] or by poor lung growth during infancy [36].

Prevalence of bronchial hyperresponsiveness in a general healthy population with normal lung volumes was 17 % [37]. Increased bronchial responsiveness has been described in 36 % of oesophageal atresia patients with tracheo-oesophageal fistula, reflecting sequelae of chronic lung disease from damaged epithelium in the airways [36]. Severe or moderate bronchial hyperresponsiveness is associated with a more restrictive ventilatory defect [28]. No correlation has emerged between increased bronchial hyperresponsiveness and history of doctor-diagnosed asthma or atopic eczema [28, 36].

Table 51.6 Self-reported incidence of asthma, allergy and respiratory symptoms of the participants with repaired oesophageal atresia ($n = 101$) and of the controls ($n = 287$)

	Patients (%)	Controls (%)	*p*-value
Impaired RSRQLI[a]	11	6	0.001
Current respiratory symptoms	11	2	0.001
Doctor-diagnosed asthma	16	6	0.001
Wheeze	37	30	NS
Allergy	42	11	0.002
Persistent cough	31	8	0.001
Pneumonia	56	20	0.001
Bronchitis	70	50	0.001
Recurrent infections	52	23	0.001
Childhood infections	35	13	0.001

[a]*RSRQL* Respiratory symptom-related quality of life index, *NS* not significant

Spinal and Other Skeletal Abnormalities

Reported incidences of vertebral and other skeletal anomalies in association with oesophageal atresia have ranged from 9 % to 24 % [23, 38–40]. The occurrence of musculoskeletal defects and scoliosis due to thoracotomy is even more common [41–43]. Many of the skeletal and hand anomalies are not evident in infancy and in childhood, and therefore, their real incidence and natural history remain unclear.

Table 51.7 Pulmonary function, bronchial hyperresponsiveness, exhaled nitric oxide and skin prick test among adults with repaired esophageal atresia ($n = 101$)

Variable	Result mean (range)	Abnormal (%)	Grade mild	Moderate	Severe
Age (years)	36 (21–57)				
Body mass index (kg/m^2)	24 (21–45)				
Spirometry					
FVC % of predicted	77 (53–120)	57 %	28 %	28 %	1 %
FEV1 % of FVC pred	100 (72–119)	57 %	25 %	29 %	3 %
Restriction		21 %	18 %	3 %	0
Obstruction		21 %	15 %	4 %	2 %
Both restriction and obstruction		36 %	10 %	25 %	1 %
Histamine challenge test					
PD15FEV1 (mg)	0.65 (0.03–1.60)	41 %	26 %	11 %	4 %
PD15FEV <0.4 mg		15 %	–	–	–
Exhaled nitric oxide elevated		11 %	7 %	4 %	0
Skin prick test positive		37 %	15 %	–	22 %

FVC forced vital capacity, *FEV1* forced exhaled volume in 1 s, *PD15FEV1* provocative dose of histamine causing a 15 % fall in FEV1, *Restriction* = FVC <80 % = Z-score ≤2.0, *obstruction* = FEV1/FVC <87 % = Z-score ≤2.0

In our adult study population, vertebral anomalies were detected in 45 %, most commonly in the cervical spine (in 38 % of the patients). Most of these were vertebral fusions in C2–3 and C6–7 (Fig. 51.2). The most significant risk factor for vertebral anomalies was any additional anomaly. Clinical and radiographical scoliosis was found in 56 % of the patients; the risk of significant scoliosis was 13-fold when compared with healthy population (Tables 51.8 and 51.9). Thoracotomy-induced rib fusion and other associated anomalies were the strongest predictors for scoliosis. The most common type of scoliosis was upper thoracic (in 31 %) (Figs. 51.2 and 51.3) and showed concavity towards the thoracotomy site. In most patients, the clinical course of scoliosis was mild and did not require bracing or spinal surgery. Radial ray anomalies were found in 25 % of the patients, of which most were thenar aplasias or hypoplasias. Few patients have had floating thumb that has been corrected successfully with pollicisation of the index finger. In the majority of the patients, the vertebral anomalies and radial ray anomalies were not detected or recorded during the initial management period and follow-up during childhood.

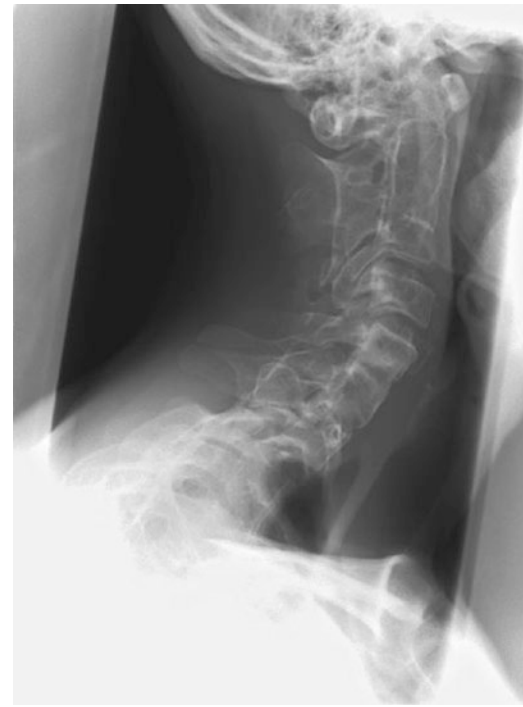


Fig. 51.2 Radiograph of cervical spine with multiple vertebral fusions and of severe thoracic scoliosis

Deformities of the chest wall and spine may result from associated vertebral and skeletal anomalies or be due to thoracotomy. Previous studies on patients with repaired oesophageal atresia have reported "winged" scapula in 24 % [45], anterior chest wall deformities in 20 % [45, 46] as well as rib fusion and female breast deformities. We found

Table 51.8 Risk for scoliosis in patients with repaired oesophageal atresia compared to controls from study of Nissinen [44]

	Patient group	Control population		
	(*N* = 100)	(*N* = 855)		
Degrees of scoliosis	*N* (%)	*N* (%)	OR (95%CI)	*p*-value
>10°	56 (56)	79 (9.2)	13.2 (8.2–21.0)	<0.001
>20°	11 (11)	6 (2.4)	37.8 (13.5–106)	
>45°	1 (1)	0		

CI confidential interval, *OR* odds ratio

Table 51.9 Characteristics of study participants and non-participants

	Participants N (%)	Non-participants N (%)
Number	101 (100)	161 (100)
Male gender (%)	58 (58)	83 (64)
Age in years, mean (range)	36 (22–56)	37 (21–57)
Body mass index, mean (range) (kg/m^2)	24 (21–45)	–
Oesophageal atresia (%)		
With proximal TOF	2 (2)	3 (2)
With distal TOF	91 (91)	120 (89)
With double TOF	5 (5)	10 (7)
Only TOF	3 (3)	3 (2)
Associated anomalies primarily (%)	30 (30)	56 (35)
Associated anomalies currently (%)	72 (72)	–
VACTERL primarily (%)	5 (5)	8 (5)
VACTERL currently (%)	23 (23)	–
Anastomotic complications (%)		
Leak	4 (4)	4 (3)
Recurrent tracheo-oesophageal fistula	10 (10)	10 (7)
Stricture requiring resection	4 (4)	3 (2)
Antireflux surgery (%)	10 (10)	8 (6)

TOF tracheo-oesophageal fistula, *VACTERL* vertebral defects, anal atresia, cardiovascular anomalies, tracheo-oesophageal fistula with oesophageal atresia, radial and renal dysplasia, limb defects

shoulder asymmetry in 80%, chest wall deformities in 15% and rib fusions in 30%. Shoulder asymmetry, "winged" scapula and limited motion of the right upper extremity result from paralysis of the latissimus dorsi muscle, and chest wall deformities from atrophy of the serratus anterior muscle, thoracotomy-induced rib fusions, scoliosis or other deformities of the thoracic cage (pectus carinatum or excavatum).

Quality of Life

The adult oesophageal atresia patients had more frequently impaired gastrointestinal (GIQLI<105 in 23% of the patients vs. 8% of controls) and respiratory-related (RSRQLI<45 in 12% of the patients vs. 2% of controls) quality of life in relation to controls ($p<0.001$). There was no difference in the total scores of disease-specific quality of life (GIQLI and RSRQLI) and in the overall health-related quality of life (SF-36) between the patients and controls.

In a previous study, adults with repaired oesophageal atresia achieved a gastrointestinal quality of life index (GIQLI) score similar to that of their general population-derived controls, and no difference in health-related quality of life, even though they had more dysphagia and GOR and a lower respiratory symptom-related quality of life [47]. In another study, one-third of the adult survivors have had negative effects of

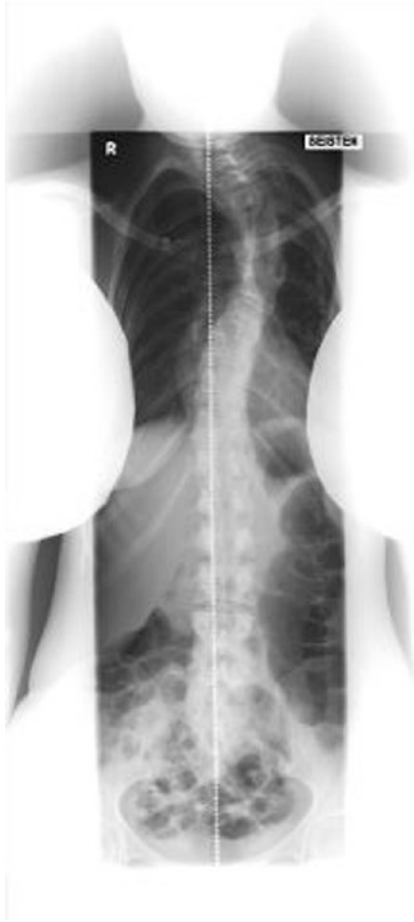


Fig. 51.3 Radiograph of cervical spine with multiple vertebral fusions and of severe thoracic scoliosis

oesophageal atresia on their daily life, especially dysphagia, but their generic quality of life, as well as physical and mental health, was good [48]. Patients reporting dysphagia more often had disturbed motility and lower scores for quality of life [48]. In a third study, the GIQLI results were similar after primary anastomosis for oesophageal atresia to those of healthy controls [49].

Conclusions

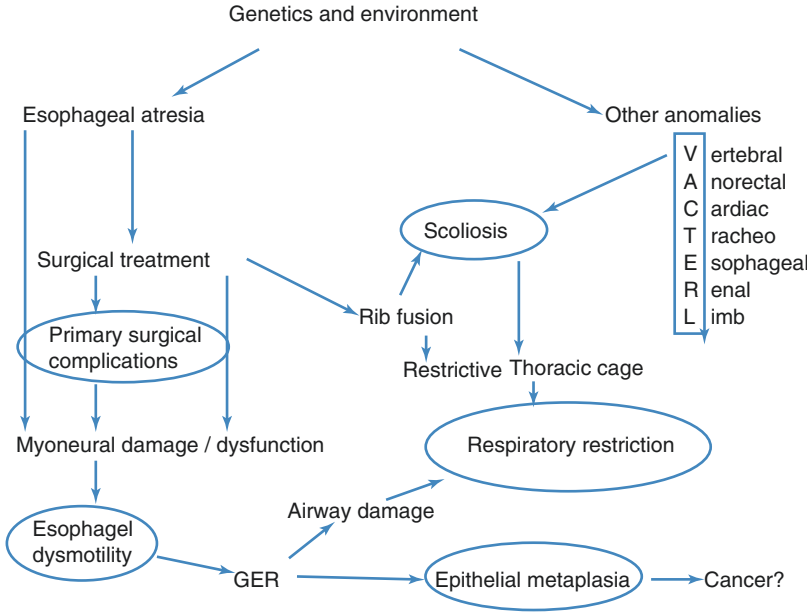
Morbidity associated with oesophageal atresia is significant in adults. Oesophageal symptoms such as dysphagia and GOR were common as well as abnormal oesophageal histology. There was no association between oesophageal symptoms and histological findings. Surgical complications, increasing age and impaired motility predicted the occurrence of epithelia metaplasia. Oesophageal anastomotic complications appeared to further impair oesophageal motility and GOR; these predisposed to the development of epithelial metaplasia that commonly occurred (21%) among adults with repaired EA. However, we found no cases of oesophageal cancer among adult study population. The overall cancer risk of adults with repaired oesophageal atresia was similar to the general population. However, the study population was relatively young; therefore, continuing follow-up and further studies are required to clarify the risk of oesophageal cancer and also define guidelines for long-term endoscopic surveillance of adult oesophageal atresia patients.

Respiratory symptoms, asthma and infections were more common in oesophageal atresia patients than in the controls. Obstruction and asthma were common, but bronchial hyperresponsiveness and restrictive ventilatory defect increased in frequency with age. Thoracotomy-induced rib fusions and GOR-associated columnar metaplasia were the strongest risk factors for restrictive ventilatory defect. Impaired respiratory-related quality of life and respiratory-related morbidity extended into adulthood in significant number of patients.

Over half of the patients with repaired oesophageal atresia developed scoliosis. Risk factors for scoliosis were 13-fold after repair of OA in relation to the general population. Vertebral abnormalities, especially cervical anomalies, and radial ray anomalies were also common; most of these had not been detected earlier. However, the overall quality of life of the patients was comparable with healthy controls.

Surgical complications, patient age and impaired oesophageal motility were significant predictors of development of oesophageal epithelial metaplasia, suggesting that a tight primary oesophageal anastomosis and reoperations due to surgical complications further impair oesophageal motility, predisposing to epithelial metaplasia. Columnar epithelial metaplasia of

the oesophagus is a preneoplastic condition arising as a result of GOR, and it remains still unclear whether the presence of intestinal metaplasia is required for neoplastic potential [50]. The patients with epithelial metaplasia showed significantly lower median wave amplitudes in the distal oesophagus as well as decreased frequency of propagating peristalsis. Thus, primary anastomosis under considerable tension and the repeated, often extensive, surgical dissection during reoperations may result in additional neuromuscular damage and predispose to further impairment in oesophageal motility, GOR and subsequent development of oesophageal epithelial metaplasia. Although definitive recommendations concerning surveillance endoscopies cannot be given based on our study, screening endoscopy may be warranted after 30 years of age at least for patients with operative complications and long-gap EA.



Flow chart of factors determining long-term outcome of oesophageal atresia

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The Minnesota Experience

52

Khalid M. Khan

Introduction

It is well known that the typical case of esophageal atresia (EA) which includes a tracheoesophageal fistula (TEF) is managed by a primary repair procedure soon after birth. Where the esophageal defect is long, a primary repair is not possible and a variety of alternatives have evolved. At the University of Minnesota, a unique procedure was developed over two decades ago as a direct response to the use of the stomach, colon, or small intestine to replace the esophagus and in the belief that the esophagus itself is the best conduit to the stomach. This procedure involved applying traction to grow the native esophageal ends to the point that a primary repair can be performed and has been used in infants with almost no discernible lower esophageal remnant. Here, we discuss the procedure and outcomes.

Background

Esophageal atresia is a congenital defect of the mid-esophagus that results in blind proximal and distal esophageal pouches that are evident at birth. In the most common variant accounting for around 70–80 % of cases, there is a fistula from the lower esophageal pouch to the trachea (type C) [1]. The length of the lower pouch is preserved as a result of tethering via the fistula to the trachea. Conversely, in infants born without a fistula to the lower end (type A or pure EA), the lower esophageal pouch is not well formed. As would be expected, the situation is similar when a fistula is present only from the proximal pouch to the trachea (type B). The most severe configuration of pure EA comprises an upper pouch that terminates in the neck and the lower segment remains below the diaphragm. In practice for the majority of type C cases with a short gap, primary repair is possible soon after birth. Gaps of 2.5–3 cm are considered long as primary repair in these cases is often not possible [2]. For the minority of patients with a miniscule lower segment that may only reach the diaphragm, a primary anastomosis is usually considered impossible [1–3].

Methodology to circumvent a long gap has included delaying the anastomosis so that some growth can occur with time. A myectomy of the circular muscle or formation of a rotating flap from the esophageal pouch has also been used to preserve the esophagus, while the miniscule lower pouch is often removed altogether and either the stomach, small bowel, or colon has been brought up to provide continuity with the upper esophageal pouch; the gastric cavity may be dissected longitudinally or including the fundus to provide a tube or pulled through the hiatus

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relocating partially in the thoracic cavity [4–6]. More recent developments include transplantation, tissue engineering, and using stem cells to reconstitute the esophagus [7].

The Minnesota Method

While the University of Minnesota has a long history in the area of transplantation, thinking in regard to repair of long-gap EA was taken in a different direction by Dr. John Foker [1, 2]. He hypothesized that the knowledge that tissue has an ability to regenerate, grow, and develop given the appropriate stimulus should be applicable to the esophagus particularly in infants. At this age, there is continuing growth and therefore the possibility that this process can be enhanced. Indeed, delayed primary closure aimed to take advantage of this process. Traction was certainly known to be an effective method for expanding tissue particularly skin though it was not implicit for a complex structure such as a viscus. Foker proposed the application of traction directly to the esophageal ends as a simple technique that is possible only in the esophageal part of the alimentary tract because the esophagus is uniquely fixed at both ends.

Preoperative Assessment and the Esophageal Gap

Assessing the gap length is a prerequisite to deciding on appropriate treatment. The standard methodology to assess the gap between the two esophageal pouches involves radiographic imaging. An upper pouch fistula can be assessed with instillation of contrast though caution is necessary to prevent significant aspiration. The presence of a lower pouch fistula is signified by air in the stomach. The absence of air in the stomach requires assessment with contrast after a gastrostomy is fashioned. The true length of the lower segment and therefore the gap length do need to be explored, and we have typically performed contrast studies while distending the two pouches with probes to have a better understanding of how the two pouches may behave intraoperatively. Even on a posterior-anterior radiograph, there may be inaccuracy in assigning gap size, and vertebral body size is used as markers of length. Ultimately intraoperative assessment with and without tension applied to the esophageal ends is the best measure of the ability to perform a primary repair and has been fundamental to the algorithm that determines the need for traction (see below). Endoscopic assessment is part of the initial evaluation of the upper and lower esophageal pouches for occult fistula and integrity of both segments (Fig. 52.1).

The Surgery

The details of the method have been published previously [1–3]. In brief, the esophageal gap is first estimated using a contrast radiographic study. The initial operative procedure is posterior right thoracotomy between the fourth and seventh ribs. The two ends of the esophagus are assessed as to whether a primary anastomosis is possible. If an anastomosis cannot be formed, sutures with radiopaque markers are placed in the ends of the two esophageal segments and traction

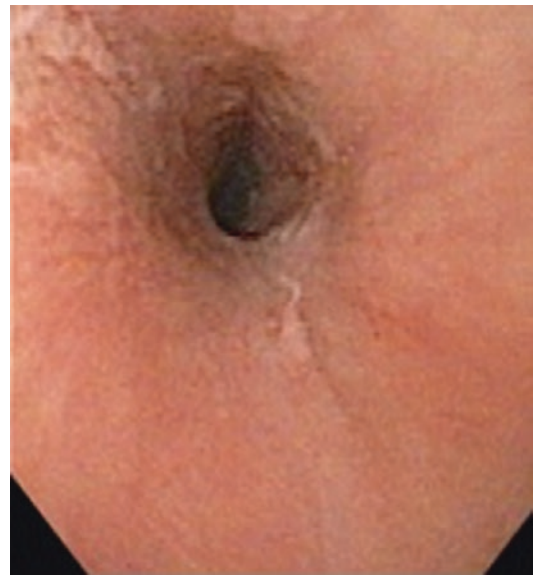

Fig. 52.1 Endoscopy through the gastrostomy site showing the appearance of the lower esophageal segment

is applied. For external traction, the sutures are crossed and brought out of the back above and below the incision and tied over silastic buttons (Fig. 52.2). The sutures are shortened up to three times per day and tension maintained until the two ends of the esophagus are seen to be close enough on a radiograph to attempt an anastomosis. Internal traction is considered for relatively smaller gaps for 3–4 days, and sutures are attached to the prevertebral fascia. Of note, the procedure was subsequently applied to long irregular caustic strictures facing the prospect of esophageal resection.

Along with the change in the radiographic appearance of the opaque markers at the tip of the esophageal segments, a reduction in the tension of the sutures signals the need to regularly tighten the traction sutures. Where there is doubt regarding slippage of the sutures, the intraoperative examination of the esophageal segments allows estimation of thickness, and endoscopy allows an examination of mucosal integrity. Furthermore, we have used ultrasound to examine the mural structure and found that it is maintained throughout the traction process [3, 8]. Of note, a separating barrier between the esophagus and the surrounding structures is placed to reduce adhesion formation. The almost constant traction applied to the esophageal segments likely also plays a role in minimizing adhesion with adjacent structures.

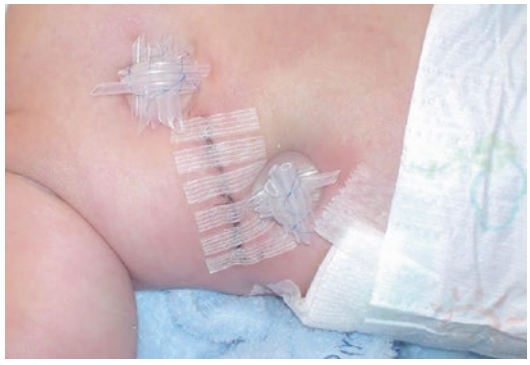

Fig. 52.2 Sutures attached to the esophageal ends are brought out of the back above and below the incision and tied over silastic tubes. The sutures are tightened frequently to maintain the tension on the respective esophageal ends

The Minnesota Series

The series comprised of patients mostly from outside of the state of Minnesota. After the initial success of the program, international referrals were also seen including the patients and the technique. Patients were in a variety of states that included having prior esophagostomy, colon interposition, and failed attempts at primary repair with a recurrent communication to the thoracic cavity. The majority of referrals were infants though those who had failed an attempt at delayed primary closure were often young children. Gaps of over 10 cm were recorded in these infants with the worse cases showing almost no recognizable lower esophageal segment. The breakdown of patients managed at the University of Minnesota by gap length is shown in Table 52.1. Of note, in the last decade, no patient has failed primary repair after traction despite gap length.

Perioperative Outcome

The extensive nature of the surgery typically means that the patient is not extubated immediately following the primary repair procedure. Anastomotic leaks are of the greatest concern following primary repair especially in our population given that the anastomosis is performed under tension. Table 52.2 outlines the problems that developed with using traction in patients with long-gap EA managed at the University of Minnesota.

A combination of contrast and endoscopy is routine to confirm adequacy of the anastomosis. Dilation is typically performed, “as needed” in

Table 52.1 Gap length of esophageal atresia cases managed at the University of Minnesota (1990–2007)

Long gap	2.6–3.4 cm	17
Ultra long gap	≥3.5 cm	70
	3.5–4.5 cm	(23)
	4.6–5.9 cm	(27)
	6.0–9.9 cm	(16)
	>10 cm	(4)
Total		87

Table 52.2 Operative complications of esophageal traction for long-gap esophageal atresia

Traction sutures avulsed/replaced	6
Traction sutures reconfigured	8
Esophageal ends freed up	1
Erosion of chest tube into esophagus (none prevented primary repair)	1

Table 52.3 Gastroesophageal reflux in patients with long-gap esophageal atresia treated with fundoplication at the University of Minnesota

Gap length	*n*	%
≤3.5 cm	17/65	25 %
≥3.6 cm	68/70	97 %

the common case of EA-TEF; however, we have learned that anastomotic narrowing is inevitable, and therefore gentle dilation is performed at 3 weeks following anastomosis. This is repeated at 2–3 week intervals based on the anastomotic appearance itself. Typically between three and five sessions, it seems to be necessary to understand whether the anastomosis will relent, and increasing intervals between assessments tend to be confirmatory. The timing of dilations and the length of time necessary to achieve an adequate lumen cannot be predicted to develop a suitable protocol for all patients as each cased differs. For difficult cases, we have started to use stenting as a technique to reduce the need for dilations [9]. We begin feeding patients as soon as possible and despite some narrowing as the eating process itself serves to help the dilation process. Not surprisingly, the longest gaps have been the most challenging not only operatively but in the extent to which they stricture. Most of our patients with extremely long gaps undergo fundoplication as there is a natural tendency for the gastroesophageal junction to be pulled in to the diaphragmatic hiatus (Table 52.3). The fundoplication is also far from straightforward given that the gastroesophageal junction has to be reestablished in the abdominal cavity.

Results

The results of the Minnesota practice have been outlined in a number of publications that have focused on the various issues that have needed to be addressed during development of the program. The earlier descriptions were focused on surgical technique and thereby proof of principal [2]. Outcomes and the clinical progress of patients have been reviewed periodically. As expected in a patient group that is characterized with major non-EA-related comorbidities, deaths were recorded in patients managed at the University of Minnesota (Table 52.4). No deaths were however related to the management of the EA itself.

Table 52.4 Deaths in patients with long-gap esophageal atresia undergoing repair at the University of Minnesota

NEC	1	Satisfactory repair
PNET	1	Satisfactory repair
Birth hypoxia	1	Satisfactory repair
Pulmonary vein stenosis	1	Satisfactory repair
Drug reaction	1	Satisfactory repair
Subdural bleed	1	Satisfactory repair

Table 52.5 Follow-up of patients with long-gap esophageal atresia >3 years after primary repair (2006)

	N = 28
Eat normally for age	27
Gastrostomy tube supplementation	3
Proton pump inhibitor	5
Diagnosis of gastroesophageal reflux	4
Pulmonary symptoms	0

The successful early management of these cases is paramount for resuming a normal course to feeding and childhood development, and to this end, we have shown that despite delays in feeding, which in some cases was years, the feeding pattern can be established without resorting to unusual diets [10]. We have not noted any tendency to aspiration or sinopulmonary problems in the short term other than those with laryngotracheal clefts, though this is a possibility given the atonic nature of the lower esophagus. However, we would not expect this to be different to the standard EA-TEF repair. Table 52.5 shows our review of a proportion of the patients after 3 years, and Table 52.6 shows the most recent data. These data indicate that gastroesophageal reflux is a possibility in a proportion of patients. Of the more recent cases, comorbidities such as chronic lung disease related to prematurity were

Table 52.6 Follow-up of patients with long-gap esophageal atresia >3 years after primary repair (2013)

	$N=20$
Eat normally for age	17[a]
Gastrostomy tube supplementation	3
Proton pump inhibitor	9
Diagnosis of gastroesophageal reflux	7
Pulmonary symptoms	2[b]

[a]One vegetarian

[b]One related to gastroesophageal reflux

noted to be an issue (Table 52.6). To put all of these follow-up issues in context, it has been well documented that even patients with delayed closure may have feeding problem, and feeding problems are not uncommon especially in patients with long-gap EA despite the type of management of strategy [11–15]. Furthermore, it has been previously shown that there is a significant chance of loosening of the wrap in patients who have undergone fundoplication after EA repair especially in long-gap EA cases [13].

The Role of the Foker Technique

Given the novel nature of the procedure described by Foker, there had to be a validation of the technique from sources other than our center, and after the initial reports, the technique has been attempted by others around the world [16]. There remains a debate as to the role of the procedure. We have argued that it represents the ideal treatment for long-gap EA. To preserve the esophagus has a number of advantages. Not only is there anatomical normalcy, but the physiological and psychological relationship to food is largely preserved. It should be appreciated that apart from the pleasure of it, eating defines growth, bonding, and socializing functions of normal development and life in general. The use of a flap or myotomy allows the continuity of the esophagus to be established; however, there is an obvious limitations to large or many myotomies in creating a mural weakness that may result in herniation of the mucosa to form diverticula. Similarly, the possibility of dissection of the pouch for elongation process has serious limitations particularly for long gaps, and similarly, a delayed repair is not likely to be possible in the truly long gap.

The concern regarding the long-term outcome in children is different to adult disease. As would be intuitive, patients undergoing gastric, colon, or jejunal transposing surgery cannot by definition eat normally [14]. The normal gastric reservoir is either bypassed or obliterated depending on the surgery. Furthermore, gastric transposition results in a conduit rather than a cavity. The issues with colon transposition further include a relatively atonic state, and the possibility of colon cancer cannot be excluded with time. Similarly, the exposure of the proximal esophagus to gastric acidity is a risk for Barrett's metaplasia. The clearance of the upper esophageal area is likely impaired in most of these circumstances though it is not known because of the small number if there is truly an adverse outcome.

The creation of a solution that will last a child's entire life has been the ultimate goal. We have always held to the notion that the comparison should be with alternatives for the management of long-gap EA and not to EA-TEF repair. Displacing any organ or tissue from its original location and function is likely to be a less than perfect solution particularly when it comes to the colon and gastric displacement. In the case of the former, we should acknowledge that colonoscopy or some form of surveillance is recommended after the age of 50 years in normal individuals in the United States, and therefore would need to be factored in. Furthermore, the loss of the normal position of the gastroesophageal junction is a major concern for intestinal metaplasia of esophageal tissue and is likely in the case of gastric transposition. Admittedly, our series lacks long-term data to quantitate any complications into adult life; however, the situation is not dissimilar with other organ use. This is partly as a result of the small numbers of such patients. Almost all of our EA patients undergoing traction required a Nissen fundoplication, and arguably a disruption of the lower esophageal sphincter mechanism after use of traction may be inevitable. A fundoplication after EA-TEF repair may result in short-term dysphagia related to the dysmotility of the lower esophageal segment [17].

Also a potential exists for missing feeding milestones following delayed EA-TEF repair [12]. We used questionnaires to assess the development of feeding skills [10]. Our findings are however unique, and long-gap EA serves as one of the few models for delayed initiation of feeding in human infants. In that regard, our findings indicate that biological feeding patterns are preserved despite significant delays in initiation of feeding. The findings are reassuring for parents of children with difficult EA-related problems.

In summary, the Foker procedure clearly has a role in the management of patients with long-gap EA. It is physiologically the most appropriate procedure and likely needs to be considered early and as a first option to derive the best results.

The Patient Perspective

The Minnesota approach to the management of EA had important implications for the families. The difficult problems of LG-EA, long strictures, and diverticula that were managed with the same principles in mind required a shift in thinking from one operation to at least two with a period of growth between them. The families had to consider the longer hospitalization than the one procedure usually required for creating an interposition graft—the alternative. Ultimately, what was of more importance in their decision, however, was the long-term benefit of one's own esophagus compared to a graft of the stomach or colon.

Parents that sought out the Minnesota program and traveled there for treatment created the program. They had access to information, first by an old-fashioned literature search for the first to come to Minnesota, soon followed by media publicity and the early age of the internet. Becoming informed is one thing; however, these early parents also needed to become their child's strong advocate and chose a new, and as yet unproven, treatment for LG-EA. Their choice often went against local medical advice; nevertheless, they were willing to travel great distances and spend considerable time in achieving the result they wished for their child. Consequently, they were the real heroes of the success of the Minnesota EA program. If these parents had not become advocates for their children, few operations would have been done at Minnesota, and surgeons elsewhere would not have noticed and continued using gastric or colon interpositions.

The first to arrive at the University of Minnesota were the "E" family—so termed for confidentiality purposes. Specifically for this section of the book, the mother recalled for us their story and accounts from other parents that she has contacted:

An ultrasound at 28 weeks into the pregnancy gave the diagnosis of EA. The local pediatric surgeons were sure a repair could be made shortly after birth; however, a study revealed LG-EA which precluded connecting his esophagus. We agreed to let him grow for 2 months to allow his esophageal ends to grow closer together she recalled. The gap widened, however, and we were given three choices for repair: gastric pull-up, colon interposition, or reverse gastric tube. These did not sound good and we began our research. Without the help of the Internet, we spent days pouring over books at the University Medical Library. Our research turned up an article written by Dr. John Foker which stated he had success in attaching the ends of EA patients even when the gap was very long. We placed a call and I informed him that our son had a gap of 5.5 cm and eight vertebral spaces. He told us he would do his best to get the ends together on the first try, but if he could not, he would perform a procedure (now known as the Foker Method) he devised for another boy just 2 months before. We waited another 2 months to see if the esophageal ends would grow; the hospital and our insurance company became impatient. During that time, we sought the opinions of five area surgeons and four of them told us the procedure would never work. Only one senior pediatric surgeon gave us his blessing and agreed to sign the paperwork needed to travel to Minnesota.

Our son was 2 months old when we arrived at the University of Minnesota Hospital, and 2 days later, the first stage was begun. Sutures were placed in the upper and lower esophageal ends, and after 10 days, his esophagus grew enough to

connect the ends. The weeks following included a Nissen fundoplication and were otherwise filled with recuperation, occupational therapy, speech therapy, and learning to eat. When we look back on our time in the hospital, it seems like a blink of an eye.

I have spoken with several families and was amazed to hear their stories which ended in Minnesota. No one had heard of Dr. Foker before our children were born, but we all came to the conclusion that the other options did not have the outcome we hoped for our child. Early on, we felt it was important to spread the good news. Our story was told on the evening news just as others who had driven to Minneapolis, unloaded their suitcases at the home of an aunt. Our story of success was also published in the Chicago-based support group, EA-TEF Child and Family Support Connection's newsletter. The Internet was new so I was pleasantly surprised to hear from families around the world that had read our story. They contacted me and told me they were thankful to hear about Dr Foker and his method.

One mother who had found my son's story on the EA-TEF website and decided on the Foker Method described how the local surgeon made the parents sign a legal document stating that the local hospital did not recommend the procedure and would not be held liable if they chose it against advice.

An Italian family recounted how they were told that their daughter would be "pretty normal" after a gastric pull-up or colon interposition. The mother wasn't willing to settle for "pretty normal." No one in Italy had heard about the Foker Method so the family petitioned their country's health system to fund the treatment in Minneapolis. Luckily, their doctors were very interested in the new procedure, and they arranged coverage by the national medical insurance. The parents invited a surgeon and anesthesiologist to join them in Minnesota to learn the technique. They accepted and the Foker Method has been performed several times in Napoli: the first center in Europe to use it.

A young man from England with a very challenging esophageal stricture demonstrated how this method was not just for infants with EA. He was born in London in 1995 with a long, severe stricture which limited him to liquids and gruels for the first 6 years of his life. After many dilations, they were referred to London's leading pediatric hospital, the Great Ormond Street Hospital (GOSH), and its top specialists. A course of dilations was prescribed, but unfortunately, the third one ruptured his esophagus. He was released after 3 weeks with the only option now being a gastric pull-up. His grandparents had a holiday home in Sanibel, FL, and by a stroke of fortune, there was a doctor from Minneapolis next door! He had heard of a local Minneapolis surgeon who had developed a new way to solve problems with the esophagus and gave them the contact information. They sent an email describing his problem. The answer was that although the growth procedure was designed for babies, it should work equally well for a child. They went back to GOSH to explain the proposed surgical treatment and were told they did not believe it was possible. It would go against all current thinking about being able to cut a section out of the esophagus and rejoin it without a lot of leakage. His mother refused to sign for a gastric pull-up. Their journey to Minnesota began without medical insurance to cover the treatment so they approached the, National Health Service (NHS) in the UK to see if they would provide funding. Because the procedure was not offered in the UK, they would only consider funding if the treatment were approved by NICE (National Institute of Health and Care Excellence). Without the support of the UK specialist, this was not forthcoming. His parents felt they had no choice but to go ahead. They spent 3 months in Minneapolis where a three-part operation over 14 days removed the long, thick, and tight stenosis. The center was taken out three times until the stricture was all removed. The principle was the same, the application just a bit different. On return to the UK, his mother continued her efforts to get the procedure recognized as an option for children suffering from LG-EA or other esophagus problems. She appeared on television and had several newspaper articles published. Eventually, it became accepted as a treatment option by NICE.

The last parents recalled how their son was born with EA in Boston in 2004. They had done some research on EA, but when they told their surgeon they wanted to opt for the Foker method, the response was "we're not going to do anything crazy." They spoke with another surgeon, Dr. Russell Jennings, at Boston Children's Hospital, and he facilitated the referral and accepted an invitation to fly to Minneapolis to learn the procedure.

All the families that recalled their experiences felt the Foker Method was the only procedure that offered a normal life for their children. Consequently as these stories illustrate, the parents that first brought their child to Minnesota had to overcome several layers of opposition. First, they had to research and determine that growing the esophagus was possible when only information and articles from Minnesota described this procedure and its success. Second, this required follow-up, more searching, and talking to other parents. Furthermore, the local doctors often advised against the growth approach. Finally, the families were dislocated and occupations disrupted. Clearly, the parents supported the growth procedure and described its success to others. Their efforts allowed the growth procedure and the Minnesota program to thrive.

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Long-Term Follow-Up and Quality of Life After Gastric Transposition

53

Lewis Spitz and Lorraine Ludman

Introduction

While we certainly subscribe to the principle that "the child's own oesophagus is best" and that the oesophagus can be preserved in a majority of cases of oesophageal atresia [1–3], we remain concerned that in some cases repeated attempts to preserve the oesophagus may be to the detriment of the child and that their own oesophagus may be a liability. In many of these children, their entire infancy and early childhood have been dominated by endless attempts to preserve the native oesophagus at all costs. Replacement of the oesophagus represents an irreversible decision to abandon further attempts at salvage of the oesophagus.

The ideal oesophageal substitute should function as closely as possible to the original structure. The patient should be able to swallow normally, consume normal amounts, and should not experience any reflux symptoms. An additional requirement in children is that the substitute should continue functioning for many years without deterioration.

Satisfactory results have been reported for all forms of oesophageal replacement [4], although the numbers reported are mostly small and long-term data are scanty.

At Great Ormond Street Hospital for children, in London in the past 25 years, we have used gastric transposition almost exclusively for oesophageal substitution. One-hundred and ninety-two infants and children underwent gastric transposition for oesophageal substitution [5]. There were 116 male and 76 female patients undergoing the procedure at a median age of 2 years (range 7 days to 17 years).

The indications for oesophageal replacement are shown in Table 53.1. Ninety-four patients were referred from centres abroad (49 %), and 62 from centres within the United Kingdom (32 %), while the remaining 36 (19 %) received all their treatment at Great Ormond Street Hospital. In total, 156 (81 %) of our patients were referred for their replacement from other centres.

A prior colonic interposition had been unsuccessful in 17 patients, six had a partial gastric transposition, three each had had a Scharli-type procedure [6] or a reversed gastric tube oesophagoplasty, and one child had a failed jejunal interposition. Previous extensive surgical attempts to retain the original oesophagus had been carried out in a total of 69 (36 %) patients.

The method of replacement [7, 8] was via the posterior mediastinum using blunt dissection in 98 patients, while 90 patients required an additional lateral thoracotomy due to extensive mediastinal fibrosis secondary to the original injury (caustic, perforation) or to previous

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Table 53.1 Indication for oesophageal replacement

Esophageal atresia	138
With distal tracheo-oesophageal fistula	76
Isolated atresia	48
With proximal fistula	12
H-fistula	2
Caustic stricture	29
Peptic stricture	9
Other	16
Achalasia	2
Laryngeal cleft	2
Congenital amotile oesophagus	2
Congenital stenosis	3
Congenital short oesophagus	1
Prolonged foreign body impaction	2
Diffuse leiomyoma	2
Inflammatory pseudo-tumour	1
Teratoma	1

attempts at oesophageal reconstruction. The stomach was placed in the retrosternal position in four patients, who previously had a failed colonic interposition placed in that site. A jejunal feeding tube was routinely inserted in patients who had not previously fed orally. A transanastomotic nasogastric tube was left in the intrathoracic stomach to provide postoperative gastric decompression. All patients with the exception of the first nine in the series were electively paralysed and mechanically ventilated for varying periods postoperatively.

Mortality: There were nine deaths in the series, a mortality rate of 4.6%. One child died intraoperatively from uncontrollable haemorrhage, five died in the early postoperative period from either respiratory (4) or cardiac (1) failure and three died over a year postoperatively, all of respiratory causes. Eight of these children had had complex courses prior to the transposition.

We believe that mortality can be reduced by submitting patients to oesophageal substitution earlier and refraining from endless attempts at oesophageal salvage. It is easy to become unduly focussed on saving the oesophagus at all costs, but repeated attempts at oesophageal salvage will substantially increase the operative difficulty encountered at the time of substitution procedure.

Anastomotic leakage at the oesophagogastric anastomosis in the neck occurred in 23 patients (12%), all except one of which closed spontaneously. The one child with a major disruption had a cervical oesophagostomy re-established. Secondary anastomosis was carried out uneventfully 6 months later. Four of these patients had undergone previous unsuccessful oesophageal replacement procedures (two colonic and two partial gastric transpositions), and nine had had multiple procedures carried out previously in an attempt to preserve their original oesophagus.

Anastomotic strictures developed in 40 patients (20%) all but three responding to endoscopic dilatations. In the three requiring stricture resection, the procedure was successfully completed via a cervical approach. In 17 cases, the original pathology was caustic oesophageal injury. Five children had previously undergone a colonic interposition.

Significant swallowing problems were encountered postoperatively in 55 patients (29%) half of whom had prolonged difficulties. Eighteen of these children had had major swallowing problems prior to the gastric transposition. The importance of sham feeding in maintaining a normal swallowing mechanism in infants having a cervical oesophagostomy for isolated oesophageal atresia where primary, or delayed, anastomosis is impossible cannot be overemphasised. The feeding difficulties can persist for many months during which enteral nutrition is provided by jejunal feeds, but improvement gradually occurs. It is important to persist with attempts at oral feeding and to try different consistencies of food. In the long term, the great majority of patients can eat and swallow normally. Although many prefer small frequent meals, those who have undergone oesophageal replacement in later childhood report a normal feeling of satiety after eating [2].

Respiratory problems: Reflux into the cervical oesophagus is common in the early months after gastric transposition. This can lead to regurgitation and aspiration especially in the recumbent position resulting in coughing episodes. It is recommended that the infant be propped up in bed and the older child sleeps on two or three cushions. The reflux may cause

mild oesophagitis for which an antacid should be prescribed.

Severe delay in gastric emptying occurred as a late complication in 16 (8.3 %) patients. Included among this group were three infants in whom an original pyloromyotomy was converted to a pyloroplasty and two who required a Roux-en-Y gastrojejunostomy. The delay in gastric emptying may be responsible for halitosis experienced by a few patients.

Dumping symptoms is frequently experienced in the early weeks postoperatively and usually responds well to simple measures such as small frequent meals, avoidance of sugar in the diet, the addition of starch as the main source of carbohydrate and separating the solid and liquid components of a meal. Dumping as a long-term problem only occurred in 2 % of cases but all eventually resolved.

Seven patients experienced problems with the jejunal feeding tube comprising leakage into the peritoneal cavity following traumatic re-intubation, volvulus, intussusception, internal fistula and adhesion obstruction.

Other complications included three infants with severe tracheomalacia, two of whom required aortopexy, two vocal cord paresis requiring temporary tracheostomy, two chylous effusions, two transient Horner's syndrome and one postoperative haemorrhage requiring re-thoracotomy.

The long-term outcome was considered excellent if the child had normal eating habits with the absence of symptoms. The result was considered good if the child had occasional dysphagia or had an altered eating habit such as a preference for a small, frequent meal. In 90 % of our patients, the long-term outcome was considered good to excellent in terms of the absence of swallowing difficulties or other gastrointestinal symptoms such as dumping or diarrhoea. Many patients prefer to eat small frequent meals. Unsatisfactory long-term outcome was present in eight patients (4.6 %), three of whom had chronic respiratory problems (CHARGE syndrome, laryngeal cleft, recurrent pneumonia). A poorer outcome was particularly associated with multiple previous attempts at oesophageal salvage. There was no evidence of deterioration in the function of the gastric transposition in 72 patients followed up for longer than 10 years.

Long-term nutritional and respiratory function [9]: Although the few children tested have a measurable respiratory compromise, they are generally asymptomatic.

The mean total lung capacity in one of our studies was around 68 % and forced vital capacity 64 % of expected. The ratio of forced expiratory volume in one second to the forced vital capacity was 87 %. This was not a longitudinal study, and therefore, it was not possible to determine whether the intrathoracic stomach was detrimental to lung growth. Of interest was that patients undergoing an uncomplicated primary gastric transposition had greater lung volumes than those subjects having a more complicated course involving multiple thoracotomies. We are aware that a bulky stomach in the chest of a child with borderline lung function may be a problem, and under these circumstances, gastric transposition may not be the optimal oesophageal substitute.

While most of our patients were in the lower centiles for weight, their heights remain within the normal range; we were unclear if this was related to their underlying problem or to the operation. Children who had caustic injury followed their previous percentiles.

Gastric emptying studies have shown that more than 50 % of both solid and liquid components of a test meal had left the stomach by the time of completion of the meal indicating that the transposed stomach act as a conduit rather than a reservoir. There is no correlation between diarrhoea or dumping symptoms and gastric empting.

It remains to be determined whether Barrett's metaplasia in the proximal oesophagus will be a longer-term problem. We have not encountered this so far but are aware of the problem when gastric tubes are used [10]. As the stomach has been vagotomised, the amount of acid produced may be insufficient to induce metaplasia.

We remain unsure of the best approach for those with CHARGE association, complete laryngeal clefts and caustic injuries to the upper

oesophagus and pharynx, as bolus gastrostomy feeds may be necessary in the long term in these children. Colonic interposition may be a better option under these circumstances.

We are encouraged that at least after the first two decades, there is no symptomatic deterioration in function of the transposed stomach.

Gastric transposition has replaced colonic interposition as the oesophageal replacement procedure of choice in many centres [5, 11, 12]. The excellent blood supply of the stomach, the fact that only one anastomosis is required and the relative technical ease of the procedure are clear advantages. In addition, the long-term follow-up of our patients has shown good growth and development and that the function of the replacement continues to be satisfactory in the immediate future.

Quality of Life Following Gastric Transposition

Previous research had shown that a significant proportion of children who underwent major neonatal surgery for life-threatening congenital abnormalities experienced psychosocial problems during childhood and early adolescence [13–16]. Since the outcome for children undergoing oesophageal replacement with gastric transposition for failed repair of oesophageal atresia has not previously been reported, we carried out a descriptive study in 2002 to assess in-depth functional outcome, psychosocial adjustment and health-related quality of life of patients following gastric transposition (GT) [17].

The rarity of the problem and the fact that many patients originated from a wide geographical area meant that our sample size was small. All the patients were resident in the United Kingdom and had undergone gastric transposition at Great Ormond Street Hospital for Children in London. Based on their operative history before gastric transposition, the 28 patients were divided into two groups. Group 1 consisted of 13 patients for whom gastric transposition was the primary reconstructive surgical procedure. The 15 patients in group 2 had undergone attempts at oesophageal repair or replacement, which had failed. Over two thirds of the patients in group 1, and more than half of those in group 2, had associated anomalies.

The total number of operative procedures for these 28 patients, including those performed in other institutions and those relating to procedures for associated anomalies, ranged from 2 to 91 (mean, 24 ± 22). The mean number of operative procedures in group 1 was 14 (SD, 15), and 32 (SD, 25) in group 2. The difference between the groups was significant ($p < .05$). In group 2, the mean number of operative procedures after gastric transposition was 19 (SD, 21) compared with a mean of 2 (SD, 2) in group 1 (Table 53.2).

Four patients (two in each group) were below school age, and eight patients (three in group 1,

Table 53.2 Patients' characteristics

	Group 1 $n = 13$	Group 2 $n = 15$
	Mean (SD)	Mean (SD)
AGE (years)	13 (5)	13 (6)
GA (weeks)	36 (3.4)	35 (3)
BW (kg)	2.14 (.54)	2.39 (.89)
Number of patients (%) with associated anomalies	9 (69)	8 (53)
None	4 (31 %)	7 (47 %)
Significant[a]	7 (54 %)	6 (40 %)
Cardiac	2	3
VATER	4	2
Sensory deficit	2 (15 %)[b]	2 (13 %)[c]
Age at GT (decimal yrs)[d]	0.95 (0.6)	4.56 (5)
Time since GT (decimal years)	12.26 (5.34)	8 (7)
Total no. of all operative procedures[b]	14 (15)	32 (25)
Related to oesophagus before transposition	1	19 (21)
Related to oesophagus after transposition	2 (2)	5 (7)
Body mass index: weight (kg)/length (m)^2 (z scores adjusted for age and sex)	−1.67 (0.98)	−1.70 (1.10)

[a]Includes conditions such as Fanconi anaemia (group 1), trisomy 21 (group 2)
[b]1 with bilateral anophthalmos and cerebral palsy; 1 congenitally blind
[c]2 with profound deafness
[d]$p < 0.05$

five in group 2) had left school. One was at university, three are at college, three were employed, and one had recently given birth to a healthy boy. Of those at school, five patients were in a special unit or in special schools, and four required special needs within normal schools (9/17, 53 %); in addition, two of the older patients had been in a special unit, and two had moderate learning difficulties (13/28, 46 %). With one exception, all the older patients, including the young mother, were still living with their parent(s).

The design of the study included a clinical review, in-depth interviews with patients and their parents and the use of self-report standardised questionnaires. For psychosocial outcomes, we used the Child Behaviour Checklists (Achenbach [18]): a questionnaire completed by parents (CBCL for patients aged 2–18 years), the parallel Teacher Report Form (TRF for patients aged 4–18 years) and the Youth Self-Report Form (YSR for patients aged 11–18 years). These Achenbach questionnaires [18–21] are designed to measure competencies and behavioural/emotional problems as seen by parents, teachers and youth, respectively, and make it possible to compare data from different respondents on a common set of problem items and scales. They have been used extensively in child/adolescent mental health research. Reliability and validity are well established. Health-related quality of life (QOL) was measured using a modified version of the Eypasch Gastrointestinal Index (GIQLI) [19, 22].

Behavioural and Emotional Outcome

The overall mean scores based on the parents' and teachers' report were similar to the norms. However, the distribution of the individual scores indicated a significant proportion of the patients in group 2 with scores in the clinical range. For example, based on the parents' report, only one (1/10, 10 %) patient in group 1 had scores in the clinical range on the total problem score, compared with 3/12 (25 %) patients in group 2 on both the total problem and internalising scales; externalising disorder scores were low in both groups. The teachers' views of their pupils differed from that of the parents. Although overall mean scores were similar to the normative data, the distribution of the individual scores indicated a significant proportion of the patients in both groups with scores in the clinical range. Depressive symptoms were foremost among patients in group 1 (3/7 43 %) and externalising disorders among patients in group 2 (3/7 43 %) [20]. The parents' and teachers' findings did not appear to be related to the presence of associated anomalies or the length of time since GT.

Twelve patients completed the Youth Self-Report Form—six in each group—and, with only one exception, they all rated themselves as functioning well within the normal range.

To sum up, based on these findings, a significant proportion of patients who underwent GT, after other procedures had failed, were judged by the adults who knew them well to have psychosocial adjustment problems. Disturbed behavioural adjustment, principally internalising disorders, was noted by teachers for a proportion of the patients in group 1.

Health-Related Quality of Life Outcomes

Nineteen patients aged between 10 and 22 years, ten in group 1 and nine in group 2, completed the questionnaire. The only difference between the groups was on disease-specific symptoms. For example, fewer patients in group 1 experienced dysphagia (30 % vs. 67 %) or pain after eating (20 % vs. 33 %), compared with patients in group 2. Similarly, a smaller proportion of patients in group 1 had gastro-oesophageal reflux symptoms such as heartburn or regurgitation during the day or at night compared with those in group 2 (40 % vs. 67 %). Some breathlessness was experienced during the day by over half the patients in each group, but breathlessness at night was more frequent in group 2. Differences between the groups were not related to the length of time since gastric transposition. These data were supported by the parents' perception of the QOL of their children. Based on parental responses, patients in group 1

experienced fewer disease-specific symptoms such as dysphagia, dumping symptoms and pain after eating. In addition, with the exception of psychological and physical/social symptoms, parents in group 1 perceived the health-related QOL of their children to be significantly better than did parents of patients in group 2.

QOL of the Young Children

The parents' responses to the questionnaire showed that they perceived the overall QOL of the five young patients, aged 2–4 years, especially for those in group 2, to be adversely affected by difficulties relating to all aspects of eating—their enjoyment of food, restrictions in types of food they could eat and the amount they were eating. However, these problems are often reported about healthy children of this age. One patient in each group (50 % vs. 33 %) experienced dysphagia, and one child (50 %) in group 1, compared with two in group 2 (67 %), experienced pain after eating. Both patients in group 1 and one patient in group 2 (33 %) were reported to have gastro-oesophageal reflux symptoms. Similar proportions experienced some breathlessness during the day. Almost half of this small group of young children (44 %) had associated anomalies, and this was an important factor affecting their lives.

Physical Characteristics

The physical growth characteristics of the 28 patients showed that, with the exception of one patient in each group, all the patients were below the 50th centile for weight, but five patients in group 1 (41 %) and two (12 %) in group 2 were above the 50th centile for height. When the standardised body mass index (z scores), adjusted for age and gender, was calculated, all the patients had a BMI below zero, ranging from –0.10 to –3.91.

Conclusion

In this study, we examined the psychological adjustment and the QOL of a small group of patients following GT for repair of long-gap oesophageal atresia. Based on the responses of the adults who knew them well, we found that psychological maladjustment was more prevalent among the patients who had unsuccessful reconstructive surgery prior to GT. Additionally, the parents of these patients viewed their overall QOL as less satisfactory compared with those for whom GT was the primary reconstructive procedure. They were said to cope less well when eating and experienced a greater number of symptoms such as dysphagia, regurgitation and dumping symptoms. The patients themselves reported greater difficulty swallowing. However, in contrast to their parents' perceptions, they viewed their overall quality of life and psychological adjustment as normal.

With one exception, all the patients and the families in this study reported that they were extremely satisfied with the outcome following gastric transposition. Based on the interviews with the patients and their parents, the patients without debilitating conditions led relatively normal lives, and many enjoyed sporting activities. However, they tended to be less socially and emotionally independent than their peers.

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The Follow-Up of the Gastric Tube

54

Gabriel O. Ionescu, Simona Gavrilescu,
and Sandu Gabriel Aprodu

Introduction

In paediatric surgery, final outcomes can only be assessed by the quality of life enjoyed by patients who have reached adulthood, and there have been several recent reports of the long-term results of oesophageal replacement performed in childhood [2, 6, 8, 10, 12, 13, 15, 25, 30, 33, 41, 47].

Our experience of 109 patients who have undergone gastric tube oesophageal replacement (GTER) during the last 34 years forms the basis of this discussion on the follow-up of patients into adulthood [5, 22, 28–31].

Principles of Long-Term Assessment Following Gastric Tube Oesophageal Replacement

After the initial post-operative period – the first 6 months – most patients are able to eat normal food without any special precautions. Particular attention is paid to the early detection of a stricture at the cervical anastomosis that might need dilatation. The establishment of normal feeding is usually rapid in those children who had surgery for intractable strictures due to caustic ingestion but can be more difficult if surgery was performed for oesophageal atresia.

All patients should be followed according to a strict protocol.

Assessment Protocol

In the first 6 months, a clinical examination should take place every 2 months at an outpatient consultation, then twice a year for the next 4 years and then annually for life.

Weight and height should be accurately recorded and compared to reference charts. Anaemia, particularly megaloblastic anaemia, should be sought and treated.

In the first 6 months, a contrast swallow with follow-through should be performed every 3 months, or earlier if there are symptoms suggesting a stricture formation, and then twice a year for 2 years. As the child grows, outpatient endoscopy might become a reasonable alternative to these contrast studies. Reflux within the gastric tube has been noticed in many contrast studies but is asymptomatic in most patients [22].

The threat of metaplastic changes in the proximal oesophagus justifies regular endoscopy with biopsies. This should be performed by an experienced endoscopist. With the gastric tube in the posterior mediastinal position, endoscopy is usually

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easy; however, if the tube has been placed retrosternally, the examination is difficult and should be done under general anaesthetic using a small calibre flexible scope. It may not be possible under these circumstances to view the entire tube, and examination of the gastric reservoir and pylorus may be impossible. Bleeding and perforation of the tube during endoscopy have been reported [4].

In the first 3–6 months, post-operative endoscopy is focused on the recognition and management of early stricture formation at the upper anastomosis but may also detect congestion or gastritis. True peptic ulcers are occasionally seen.

Reflux within the gastric tube can be demonstrated in most patients but is frequently asymptomatic. Twenty-four-hour pH monitoring is unreliable as it cannot differentiate between refluxing acid and acid secretion within the tube [22].

In our experience pH monitoring was only used on ten occasions. These patients complained of unpleasant regurgitation of partially digested food during the night. In three patients this was severe enough to awaken the patient but caused chronic cough due to micro-aspiration in the remainder. These symptoms were controlled by sleeping in the semi-Fowler position, and they tended to improve with time. We found no benefit from the use of H_2 receptor antagonists, proton pump inhibitors, or prokinetic agents. Alkaline bile reflux, so common after total gastric transposition, was not detected following RGTER.

Late Complications Following Gastric Tube Oesophageal Replacement

Rare complications such as bronchogastric tube fistula [1, 22, 42] have been reported, and in one case this occurred many years after operation [1]. A stricture progressing to complete obstruction [40], perforation of an acquired diverticulum [40], and mucocele of the unresected injured oesophagus [31, 32] have also been reported (Figs. 54.1 and 54.2).

There have also been reports of peptic ulceration within the gastric tube [4, 11, 39, 46, 49] or peptic ulceration within the gastric reservoir [46]; most of these patients, as were three of our own patients, were successfully treated with proton pump inhibitors.

In our experience one patient presented with peptic ulceration within the gastric tube. One further patient had true gastric ulceration, and one

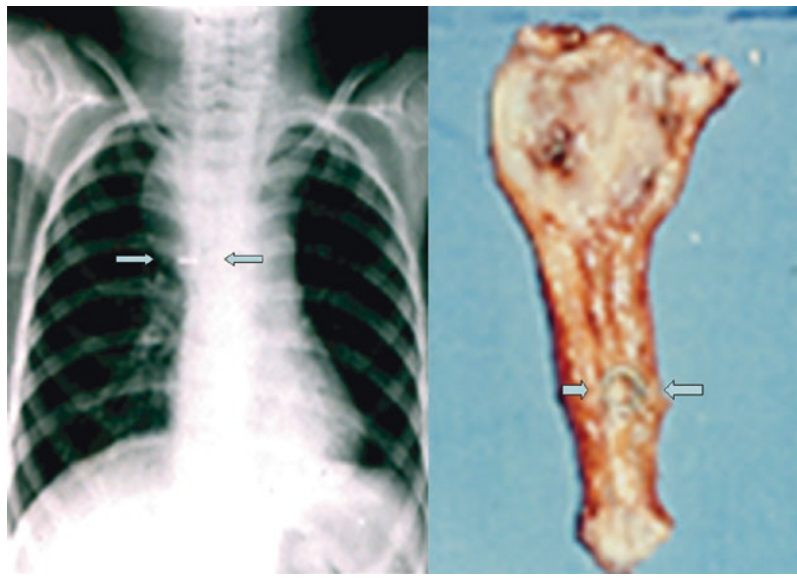

Fig. 54.1 Mucocele within the unresected injured oesophagus with retention of a foreign body inside (small metallic ring). Specimen of resected oesophagus by right thoracotomy)

patient had Zollinger-Ellison syndrome which presented many years after successful RGTER for caustic stricture with multiple recurring peptic ulcers, a perforated duodenal ulcer and a gastrocolic fistula with further ulceration in the fundus. After several operations, she finally had a gastrectomy with anastomosis of the tube to the jejunum. A preoperative celiac trunk angiography has been performed to identify the vessels of the gastric tube.

Post-operative adhesive obstruction occurred in five patients 6 months to 7 years after surgery. All were successfully treated by simple laparotomy and adhesiolysis. All five patients were seen early in our experience when, as Pr. D. Gavriliu originally recommended, we performed extensive mobilization of the splenic flexure and spleen. We no longer consider this step necessary.

In one patient 8 months after successful RGTER, progressive dysphagia occurred. This appeared due to angulation of the intra-abdominal portion of the tube that had been made too long. An anastomosis was created between the lower part of the tube and the gastric fundus after which normal feeding was restored (Fig. 54.3).

Lindhal [35] and Bornon [11] have both reported the presence of Barrett's oesophagus in mucosal biopsies above the oesophagogastric anastomosis. This would suggest that surgery has created a pre-malignant condition. However, Barrett's oesophagus, and its attendant risk of cancer, is defined as columnar-lined intestinal epithelium with various degrees of maturation and dysplasia [45]. Linthal [35] Bornon's [11] reports recognize the migration of gastric cells into the cervical oesophagus which, without dysplasia, is not associated with an increased risk of malignancy. To date there are no reports of cancer occurring either in or in relation to a successful gastric tube.

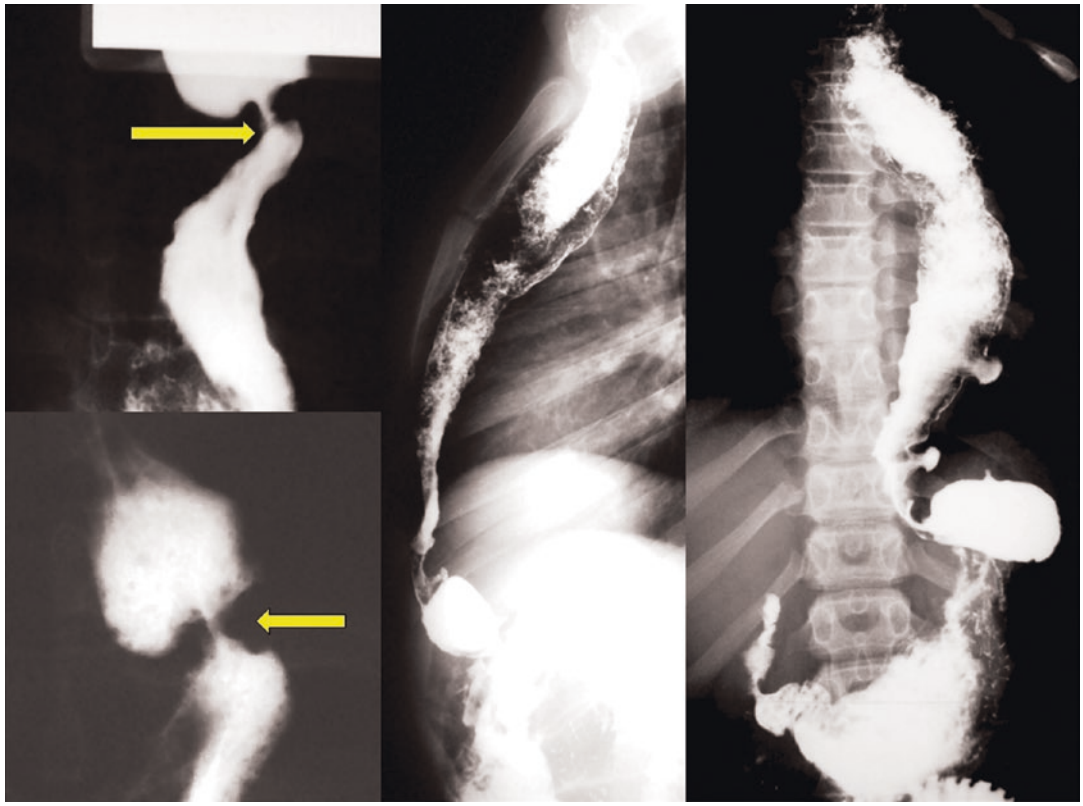

Fig. 54.2 Severe anastomotic stenosis with multiple diverticula 11 years post RGTER

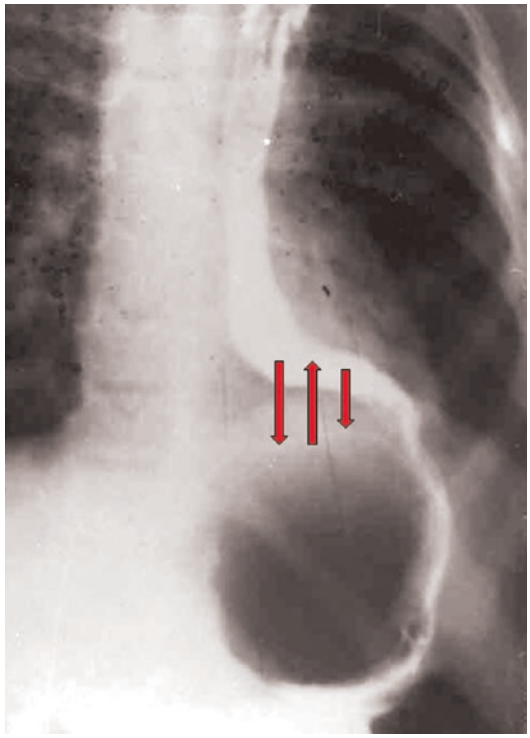

Fig. 54.3 Dysphagia due to too long angulate intra-abdominal GT

The Gastric Tube: Long-Term Follow-Up

Unlike a colon graft which tends to dilate and become redundant with time, often leading to late malfunction [19, 26], the gastric tube remains remarkably constant. Clearly the gastric tube should be constructed to match the calibre of the native oesophagus as there is a direct relationship between the width of the tube and the quality of swallowing [9] (Figs. 54.4 and 54.5).

Dilatation of the gastric tube was observed in only three of our patients, all of whom had retro-sternal placement of the tube. Dilatation was identified on routine radiological studies and was asymptomatic (Fig. 54.6).

In 18 patients oesophageal diverticula were identified on contrast swallows, but on endoscopy only 6 could be directly observed. Most developed in retro-sternal tubes that had been handsewn. Their cause and significance remain unclear, but there have been reports of bleeding and perforation related to diverticula [20, 21]. No gastric tube created with stapling devices has resulted in diverticulum formation.

Lengthening or Growth of the Gastric Tube

Despite the growth spurts of adolescence, the gastric tube appears to grow in proportion to the patient, although it is not clear that this is true growth rather than stretch. Gastric tubes can be expected to lengthen by about 1 cm per year in both the thoracic and abdominal components.

In a young girl operated upon at the age of 6 years for caustic injury, the gastric tube kept pace with her growth to an eventual 1 m 79 cm in height (Fig. 54.7).

The Gastric Reservoir: Long-Term Follow-Up

It is crucial to the success of the operation that the gastric reservoir retains its size, capacity and function after creation of a gastric tube, and this is difficult when the operation has been performed in infancy. The gastric phase of digestion, Vitamin B_{12} absorption and normal gastric emptying are all essential to normal nutrition. Both gastric tube oesophageal replacement and colonic interposition retain a gastric reservoir. Total gastric transposition greatly impairs reservoir function, particularly when augmented by a pyloroplasty or other gastric drainage procedure, resulting in a gastric phase reduced to 5 or 10 min [17, 36, 41]. A large stomach that allows creation of a gastric tube whilst leaving an adequate reservoir is an essential precondition to GTER and in patients with oesophageal atresia, in whom the stomach is initially small, may considerably delay surgery (Fig. 54.8).

Although in some patients the stomach may appear small after creation of a gastric tube, and this may be reflected in symptoms of diarrhoea and failure to thrive, growth results in normalization of gastric capacity within a year. During this transitional phase, dietary manipulation under

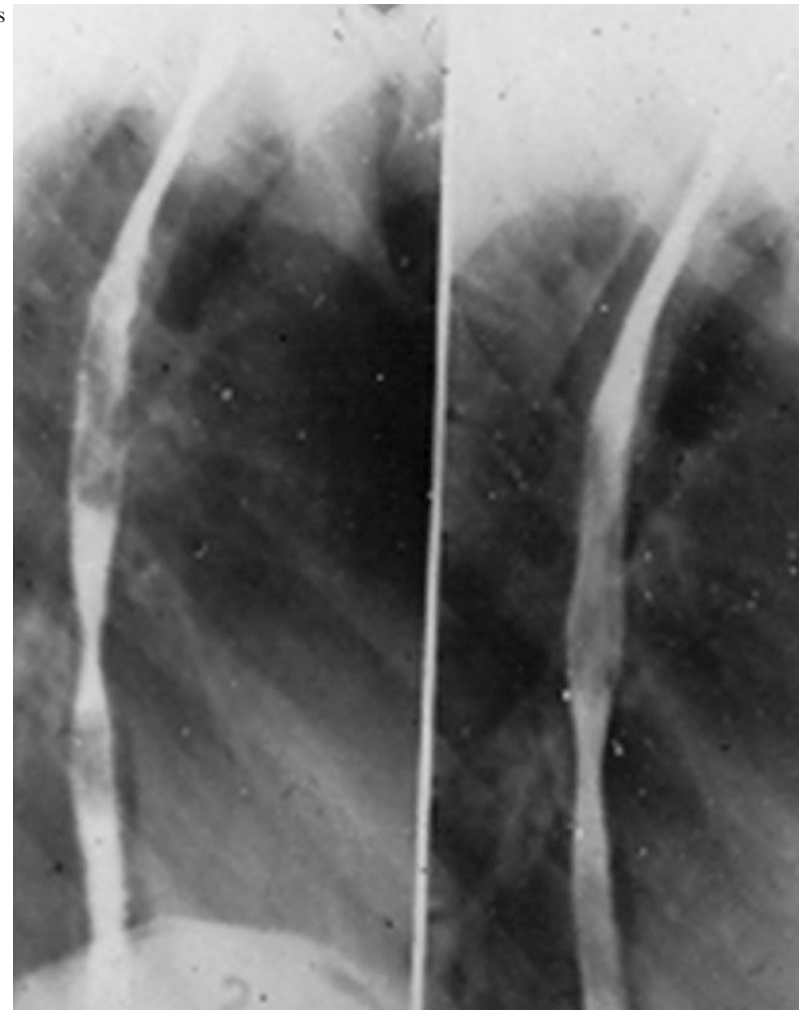

Fig. 54.4 Ideal GT 11 years post RGTER within post mediastinum

the supervision of a dietician may control symptoms. In patients with oesophageal atresia, despite sham feeding, oral feeding can be difficult to establish. Assistance can be gained from an experienced speech therapist.

Quality of Life in Adults Who Had Gastric Tube Oesophageal Replacement in Childhood

Introduction

There is copious literature to define the quality of life after oesophageal replacement performed in adults for benign or malignant disease [15, 34, 37, 48, 49]. In children several recent reports define the long-term effects of colon interposition [10, 16, 25, 38, 43, 47], gastric tube oesophageal replacement [4, 5, 15, 20, 22, 23, 30, 34], gastric transposition [17, 24, 36, 41, 44] and small bowel interposition [14].

Our experience of 109 gastric tube replacement and 37 colonic interpositions is presented.

Summary of Authors' Experience

From 1975 to 2009, we performed 109 GTER operations for long-gap oesophageal atresia

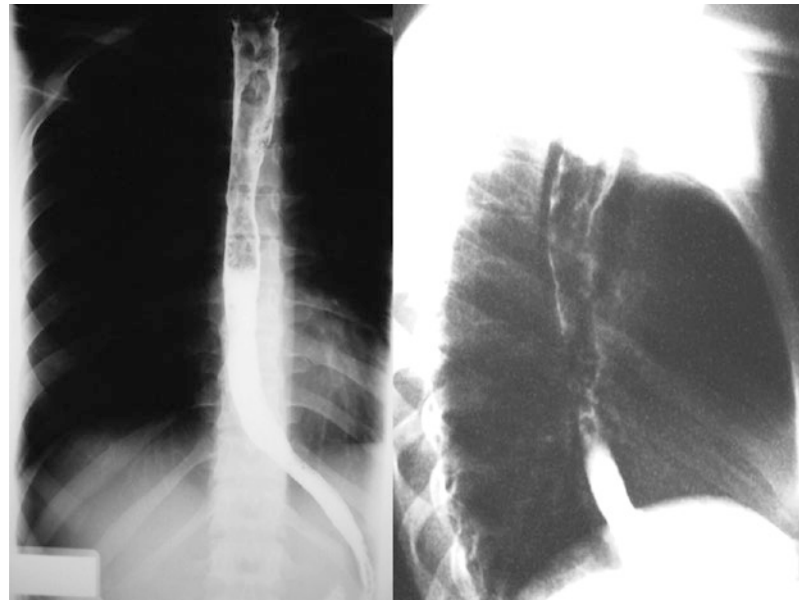

Fig. 54.5 The GT maintains the same calibre 16 years post GTER posterior mediastinum

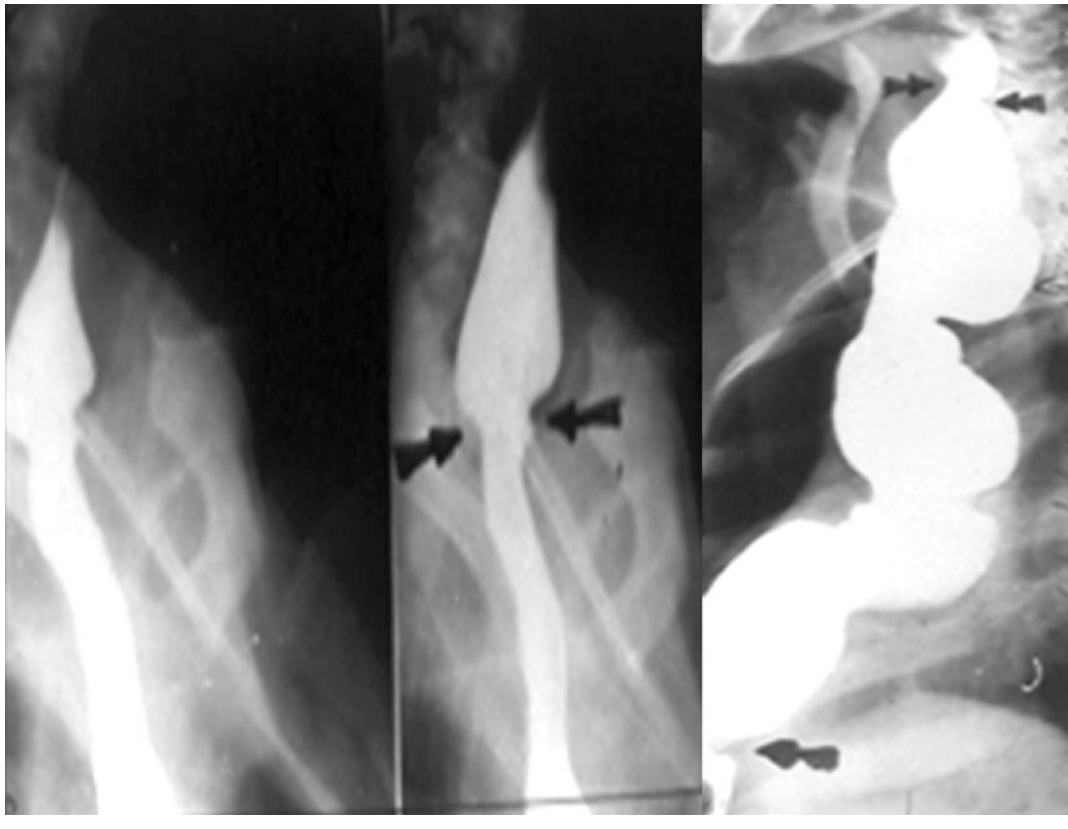

Fig. 54.6 Progressive dilatation of retro-sternal GT

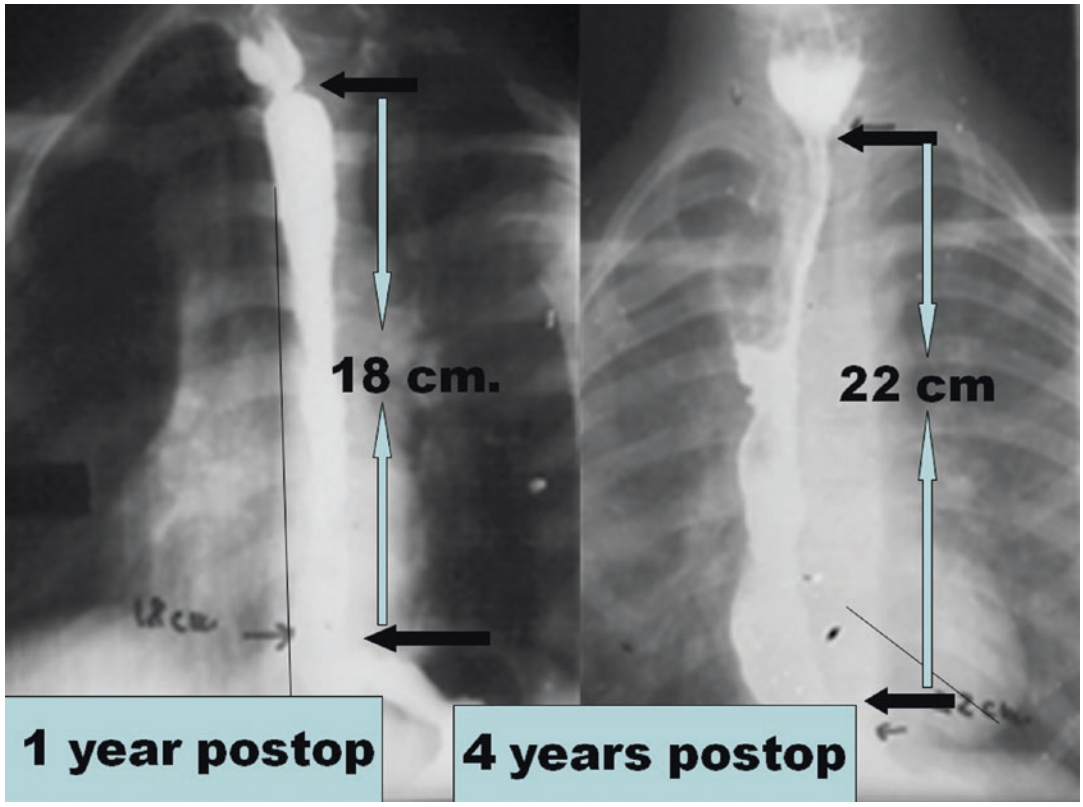

Fig. 54.7 Growth of the GT

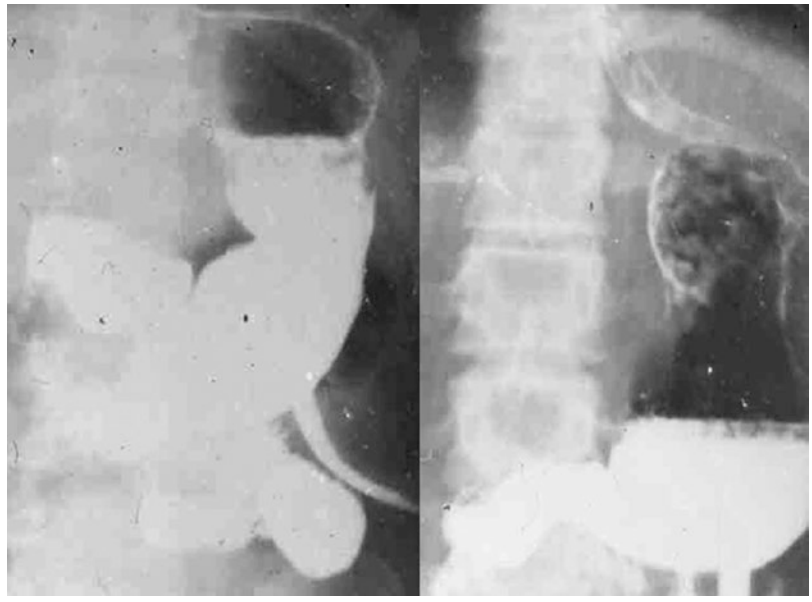

Fig. 54.8 Contrast study of the stomach immediately after GT shows good volume

(23, 21 %), severe caustic stricture (85, 78 %), including one attempted suicide, and one due to severe stricture secondary to gastroesophageal reflux.

In the first 19 patients, the tubes were sited retro-sternally without oesophagectomy, but the last 90 patients had posterior mediastinal placement with simultaneous transhiatal oesophagectomy for those with an injured oesophagus.

Two gastric tubes were isoperistaltic and 107 reversed. The detailed technique of the operation, as well as the potential complications, has already been presented.

The post-operative course was uneventful in 62 patients (53 %). Thirty-six patients (30 % suffered minor complications, and 11 (17 %) had major complications.

The most frequent complication was fistulation from the upper anastomosis, but this decreased from 37 % when the tubes were placed retro-sternally to 6 % when the tube was placed through the posterior mediastinum.

Complete failure of the gastric tube occurred in two patients: on one occasion due to the creation of an atypical tube when scarring of the greater curve due to the original caustic ingestion was identified at surgery. This ischaemic tube was removed from the posterior mediastinum on the seventh post-operative day and replaced with a retro-sternal colon interposition. One failure, in a child with severe developmental problems and hydrocephalus, who weighed just 3,5 kg at 2 years of age, was due to a breakdown of a retro-sternal tube. The child died of systemic sepsis after an attempt to repair the gastric tube via a median sternotomy.

Overall there were 7 (6 %) deaths in our experience. Five patients died following post-operative complications in the early period of the series (last 1982), and two patients died unexpectedly on day 14 and day 45 post-operatively whilst at home on full oral feeds. One of these children had Down's syndrome, and both operations were done for long-gap oesophageal atresia. It is likely that both deaths were due to aspiration during sleep.

One patient with a successful pharyngoesophageal replacement died of complications of his tracheostomy 2,5 years after a reversed duodenogastric tube for pharyngoesophagoplasty.

Prospective Study of QOL of Adults After Oesophageal Replacement Performed During Childhood

The gastrointestinal quality of life index [18] has been utilized but has proved inadequate for the assessment of quality of life after GTER. We therefore designed a questionnaire assessing the following features:

1. Medical assessment on an outpatient basis
2. Long-term follow-up
3. Social and family life
4. Extra-professional activities
5. Self-assessment of quality of life

Using this template, 86 patients were serially reviewed in 1992, 1996, 2002 and 2009. The detailed results were published as part of a doctoral thesis defended in 2009 [22].

To be included patients had to be more than 10 years post-operative and older than 16 years. From the cohort of 86 patients, 37 (41 %) fulfilled all the inclusion criteria. Nine adult patients now live and work abroad, but all completed the questionnaire and underwent clinical evaluation at their place of residence. Of the study group, the mean follow-up is 19 years. Too few patients who had GTER for long-gap atresia are represented, and it was not possible to compare outcomes for the two major surgical indications.

Questionnaire for long term follow up of patients with gastric tube esophageal replacement:

Pt. No…… Year……

Pt details……..…

……..…

Short summary……..

Age at operation……Year…….RGTER Type I /II Years from operation……..

Complications minor / major: Yes /No. If yes which one? ……

Secondary surgery for complications:

……

Follow up. Admission…….. Telephonic interview……

Weight……..Kg (under weight / normal / overweight)

Height…….cm (underweight / normal)

Swallowing /eating. Normal……..Dysphagia: minor, major, intermittent, and continuous for solid food or liquid food. Other abdominal G-I symptoms/complains……..

Dumping syndrome -Yes /No. Details……

Stool, G-I motility: normal, constipation, diarrhea, other symptoms or complaints:

……

Other minor / major health problems unrelated to the RGTER……

……

Gastric tube reflux: Yes /No/ Clinical manifestation: Yes /No……. Day /Night or Both:

Gastric - tube reflux demonstrated by contrast study Yes / No……

Other minor / major problems related with RGTER……

Anemia: Yes / No. Contrast study: Yes /No When was the last contrast study done:

……

Total proteins: Yes /No……Albumin Yes /No……..

Endoscopy: Yes /No. When the last endoscopy was done? (year)……

Biopsy: Yes /No……

Gastric endoscopy +/- biopsy: Yes / No……

Pulmonary symptoms……

Other complaints (i.e. fatique, hypoglycemia,)……

Long term follow up (2009 assessment)

1. Training, education, schools: primary school, secondary school, high school, Technical/ professional school, Technikon, University/Faculty degrees. If yes give details:

……

Did your operation in childhood influence your orientation as career choice: Yes/ No

……

Have your choice of profession been influenced by the operation: Yes /No. ……..

Have you been able to study or specialize in what you wanted without difficulty related to the operation? Yes/ No……

Profession: What is your present job?

How long have you been in this position?

Have some symptoms or other inconvenience related to the operation and are they any negative effects on your profession? Yes /No……..

Have you had to take sick leave due to the previous operation; Yes /No/ If yes, why?

……

Social and family life.

Are you married Yes /No. For how many years?.....Do you have children Yes /No……..

How many……Do you think that your family life has been influenced in any way by the previous operation Yes /No……

If unmarried do you think it is due to your previous operation Yes ?No……

Do you have a partner Yes /No……..

Do you have a normal sexual life (voluntary answer) Yes /No……

Your sexual life was or is in any way influenced by the previous operation Yes /No……

Do you have psychological or psychiatric problems which could be explained or correlated with your previous operation Yes/No: ……

Extra professional activities

What are you doing and enjoying outside of your professional work: Reading Yes/No…… Listening to music Yes /No……. Watching movies on grand screen Yes /No……..

Watching matches Yes /No…… Do you attend live theatre Yes / No. ……

Other activities……..

Are these extra-professional activities in any way influenced by your previous operation?

Yes /No…… Do you think that the fitness activity or sport are in any way influenced by your previous operation Yes /No……

Do you have a driver license Yes /No…….. Do you drive a car Yes/ No……..

In a stress condition (at home or at work) do you have symptoms related with your previous operation (i.e. difficulty in eating, true dysphagia) Yes /No ……

Any other medical or non medical problems which you think are related with the operation and not mentioned above, please comment: ……..

……

What is your own perception about the quality of your life (related or unrelated to the operation of esophageal replacement): Normal (very good), Good, Satisfactory, Poor.

Thank you for your participation.

Summary of Long-Term Results

Thirty-two (86 %) of our patients have normal swallowing, and five complain of occasional "sticking". One patient complains of symptoms of dumping but with normal gastric emptying on contrast studies. Eleven patients (30 %) were underweight and six (16 %) were short or stunted. Nine patients complained of easy fatigue that they ascribe to their surgery, and four patients reported feeling "stressed" by their situation.

Thirteen patients (35 %) have a high school or university education; 22 (59 %) are employed in a variety of trades and professions (drivers, carpenter, construction industry, agriculture). They have no complaints concerning their previous surgery. Two patients are currently unemployed.

Four female patients are married with children, one of them being the patient who attempted suicide by caustic ingestion at the age of 14 years.

Only four patients (11 %) have regular extramural activities such as sport. From the entire group, only 2 (5 %) consider that the oesophageal replacement is having a negative effect on their quality of life.

Thus, overall 17 patients (46 %) have a normal life, and 16 (43 %) have intermittent minor complaints, but they consider themselves to be leading normal lives. Four patients (11 %) have various moderate problems related to their surgery, but they are still satisfied with the results. No patients are considered to have had a bad result or to be complete failures. All eat a full diet orally, and no patient has a residual gastrostomy.

Final Commentary on Oesophageal Replacement

It is clear that three techniques of oesophageal replacement dominate surgical practice around the world: colonic interposition, gastric tube oesophageal replacement and total gastric transposition. Surgeon preference and experience are the most important factors in selecting the procedure. In very few cases, usually after failure of the primary procedure, there are specific indications for an alternative.

It is also clear that oesophageal replacement is less frequently necessary today than in previous decades due to the success of oesophageal lengthening procedures (Foker's or Kimura's techniques) applied to children with long-gap atresia. Serial balloon dilatations and intralesional steroids have also allowed oesophageal salvage in some cases of caustic injury, the incidence of which has been reduced in developed countries by legislation on the purchase and storage of caustics.

Colonic Interposition

Around the world this is probably the most popular technique of oesophageal replacement in children [10, 13, 16, 25, 38, 43, 47]. Surgery can be performed early in life, even in the presence of a small stomach, because the gastric reservoir is fully retained. An initial feeding gastrostomy is only indicated if preoperative nutritional supplementation is necessary. Colonic interposition is a good salvage procedure following failure of gastric tube oesophageal replacement [25]. It is possible after a failed gastric transposition to relocate the stomach in the abdomen and to still perform a colonic interposition [25].

As in all techniques of oesophageal replacement, the commonest complications occur at the upper anastomosis. Complete failure of the interposition is still a threat but with experience is reduced to an occasional complication [3]. With colonic interpositions, concerns relate to the long-term changes within the graft; redundancy [26], hypoperistalsis and progressive dilatation [3], a non-functional conduit [19], stasis of food within the graft resulting in halitosis due to stagnant fermented food being retained and difficult endoscopy in redundant and particularly retro-sternal grafts are the most frequently reported difficulties. Peptic ulcers due to acid reflux into the conduit and the development of diverticula have also been described [43]. Of course in very specific circumstances, a colonic interposition would be inappropriate (associated Hirschsprung's disease, anorectal malformations or acquired colonic diseases), and an alternative replacement should be performed.

Total Gastric Transposition

This procedure is frequently performed in adults suffering from carcinoma of the cervical or thoracic oesophagus and has been used by Lewis Spitz in London [17, 24, 36, 41, 44] and quickly adopted by paediatric surgeons around the world as a safe and easy means of replacing the injured or absent oesophagus. It can safely be performed laparoscopically.

The long-term results are satisfactory in many patients [17, 36, 41], and after 20 years 90 % of patients have a good or excellent result [41]. However, total gastric transposition completely eliminates the gastric phase of digestion, and contrast studies show a 5–10 min gastric emptying time. Frequently, especially if a pyloroplasty or other gastric drainage procedure has been added, there is massive bile reflux into the stomach with episodes of bilious vomiting.

Our experience of patients who have had gastric transpositions performed elsewhere suggests a failure to grow normally, probably related to the functional gastrectomy and the alteration of the stomach's function from reservoir to conduit. In our practice total gastric transposition is a salvage procedure to achieve oral feeding [3].

Gastric Tube Oesophageal Replacement

From the literature approximately 4,000–5,000 children worldwide have had gastric tube oesophageal replacement over the last 60 years [4, 5, 15, 20–23, 30]. Most were performed as reversed antiperistaltic tubes and a few isoperistaltic [11]. Our experience, over 35 years, is amongst the largest reported, with follow-up into adulthood [5, 22, 29–31].

Advantages of the Gastric Tube

The gastric tube allows flexibility in its construction, both in terms of length and calibre, to produce a well-vascularized and reliable conduit that will retain its proportions but grow with the child. The risk of infection is reduced by acid secretion within the conduit.

Using mechanical stapling devices, the creation of the tube is quick and easy as well, and the risk of leakage from the long staple line is much reduced over the historical handsewn anastamosis.

The gastric reservoir and its physiological function are preserved, and when the conduit is placed in the posterior mediastinal position, the final radiological anatomy of the upper gastrointestinal tract is near normal.

Disadvantages of the Gastric Tube

The need for a large gastric capacity before creation of a gastric tube has been repeatedly emphasized. A feeding gastrostomy for a prolonged period is necessary in most cases, particularly in long-gap oesophageal atresia.

When the operation is done without a prior gastrostomy, the completed operation resembles a bariatric procedure (sleeve gastrectomy), but the stomach develops a reservoir function over the ensuing year or 2.

The major problem with gastric tube oesophageal replacement remains the upper cervical gastric tube oesophageal anastomosis with the risk of fistula, stenosis and occasionally necrosis of the distal 1–3 cm of the tube. Most of these complications can be reduced with care and experience.

A strict protocol of follow-up is required for the early detection of anastomotic stenosis, but up to 50 % of patients will, at some stage, require dilatation which we prefer to perform using balloon dilators.

Other rarely reported complications include megaloblastic anaemia, permanent small stomach, delayed gastric emptying, dumping syndrome and Barrett's oesophagus. Apart from one child with dumping syndrome following an isoperistaltic tube, none of these complications were seen in our experience.

What Is the Best Oesophageal Replacement in Children?

Several retrospective and prospective studies [12, 13, 15, 21, 27, 43, 44], including our own [22], have attempted to answer this question. In an

extensive literature review, Arul [7] found that in the absence of prospective randomized studies, no reliable answer could be proposed.

Several authors (Burgos for colonic interposition [12, 13], Tannuri for colonic interposition and gastric transposition [43, 44], Helardot for gastric tube oesophageal replacement and other methods of oesophageal replacement [27]) have tried to establish criteria for the selection of the technique for oesophageal substitution.

Collard [15] demonstrated experimentally advantages for gastric transposition over gastric tube oesophageal replacement, and Tannuri [44] in a clinical series found superior results with the use of whole stomach. However, all studies report only early complications such as fistula formation, the number of days that ICU care is required and the need for ventilatory support, time to oral feeding, etc. The true value of an oesophageal replacement must evaluate the long-term results.

However, it is clear that there is no ideal oesophageal substitute, and with the diminishing numbers of children requiring oesophageal replacement, certainly in developed countries, it is unlikely that prospective randomized trials will be possible.

Conclusion

In children who require oesophageal replacement for congenital or acquired diseases of the oesophagus, the reversed gastric tube oesophageal replacement, brought through the posterior mediastinum in a one-stage procedure following transhiatal oesophagectomy if necessary, is an excellent option. The operation itself, as well as the preoperative preparation and post-operative monitoring, should be performed in a specialist centre by a multidisciplinary team.

The initial good results are durable, as is the anatomy and function of the gastric tube. Follow-up into adulthood shows that quality of life for most patients is excellent.

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Long-Term Follow-Up After Gastric Reconstruction of the Esophagus

55

Sarah E. Billmeier, David I. Soybel, and Michael T. Jaklitsch

Introduction

The stomach is one of the most commonly used conduits for esophageal replacement. Restoration of gastrointestinal continuity may be undertaken for a variety of underlying etiologies, including long-gap esophageal atresia in children or benign or malignant disease in adults. Regardless of underling etiology, the replacement esophagus must be able to adequately mimic the native esophagus over the lifetime of the patient. While the literature on long-term follow-up after esophageal replacement is somewhat limited, the published experience does highlight outcomes that result from the act of transposing conduit into the altered physiological environment of the chest. In this chapter we will review these outcomes, with particular focus on the results after gastric pull-up.

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Indications

The majority of esophageal procedures in children and infants are performed for esophageal atresia or strictures caused by caustic ingestions. Between 92 and 97 % of esophageal atresia defects can be corrected by primary esophagoesophagostomy [1, 2]. While even patients with long-gap atresia, defined as a gap of more than 3 cm, can be repaired primarily, a small percentage of children with atresia will be treated with esophageal replacement, either as a first procedure or after primary repair has failed. Caustic ingestion strictures are usually managed with serial dilation; however in severe cases with multiple, long strictures, esophageal replacement may be the best option [3]. The median age of esophageal reconstruction in children is dependent on the underlying disease, but is 2 years old when all etiologies are included [4]. The goal of esophageal replacement in children is maintenance of function for 70 years or more.

In adults, 74 % of esophageal replacements are for malignant disease [5]. Despite overall 5-year survival rates of 23–31 % after esophagectomy for cancer, every patient undergoing esophagectomy for malignancy has the potential to be a long-term survivor [6]. Given that the median age of diagnosis of esophageal cancer is 68, the expectation of durability for the neo-esophagus has traditionally been less than in children [7]. With advances in surveillance and management of esophageal cancer, however, adult esophagectomy patients will

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increasingly rely on an esophageal replacement for decades rather than years.

In benign disease, esophageal replacements are typically performed on younger patients with a lower risk of death from their underlying disease and thus also require long-term use of their esophageal replacement. Esophageal reconstruction for benign disease in adults is most often undertaken for esophageal strictures (42%), primary motility disorders (33%) including achalasia, perforation (14%), or paraesophageal hernias (6%). The median age of esophagectomy for end-stage benign disease is 44–55 years old [8, 9]. Esophagectomy in these patients can be technically challenging as patients have frequently had multiple previous endoscopies, dilations, or esophageal operations [9].

Characteristics of the Ideal Esophageal Replacement

The best choice of conduit for esophageal replacement has long been debated. Conduit choice must be adapted and optimized for each patient depending on the patient's anatomy, disease, and prior surgical history. The goal of the esophageal replacement conduit is to mimic the function of the native esophagus for the lifetime of the patient. An ideal conduit allows for swallowing without aspiration, eating and drinking at a normal rate, belching, and vomiting. Additionally, the conduit should form a barrier against reflux. Finally, the operation to replace the esophagus should have minimal associated morbidity and mortality [10]. Choices for conduit include stomach, colon, jejunum, revascularized free grafts of abdominal viscera, skin or myocutaneous flaps, and historically external bypass with a prosthesis. The first three options are the most common and will be discussed further here.

The Stomach as Conduit

Stomach is the most common source of conduit for esophageal replacement due to its relative operative safety and simplicity. In children, gastric transposition is associated with the least short-term morbidity and mortality relative to alternatives such as colonic transposition or gastric tubes [11–16]. With division of the left and short gastrics, the stomach can reach the level of the cervical esophagus with maintenance of blood supply via the gastroepiploic vascular arcade. Only a single anastomosis is required, and thus there is one site with the potential to leak or stricture. An illustration of esophagectomy with gastric reconstruction is shown in Fig. 55.1.

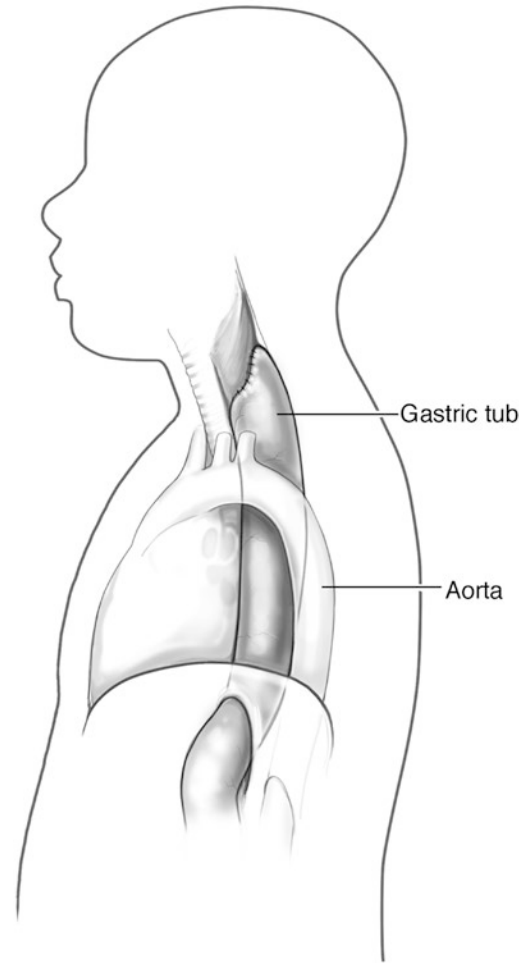

Fig. 55.1 Esophagectomy with posterior mediastinal gastric tube reconstruction and cervical anastomosis (Artwork by Marcia Williams)

The stomach has been used in a variety of configurations. Transposition of the whole stomach involves division of the left and right gastrics and left gastroepiploic and short gastric vessels and

mobilization of the pylorus and duodenum via a Kocher maneuver, followed by the creation of the anastomosis. Vascularization is based on the right gastroepiploic artery alone. A pyloroplasty or pyloromyotomy is commonly added, although this is controversial. The transposed stomach can be placed substernally or in its native bed in the posterior mediastinum.

Alternatively, a gastric tube created from the greater curvature of the stomach can be used. The gastric tube is less bulky than use of the whole stomach and passes with minimal compression through the diaphragmatic hiatus and the thoracic inlet into the neck. In our experience, the width of the gastric tube impacts the ability of the conduit to efficiently transport food, with a width of two fingers breadths conferring optimal function.

Disadvantages to the use of gastric conduit include the possibility of immediate morbidity due to vascular insufficiency at the level of the anastomosis. Over the longer term, the lack of a reflux barrier between the stomach and the esophagus can lead to complications such as aspiration, esophagitis, and stricture [17]. However, as originally observed by Sweet in 1945, the higher the anastomosis, the lower the incidence of significant reflux [18]. Disadvantages of gastric tubes include the possibility of leak along a long staple line and risk of injury to the spleen during preparation of the tube.

Alternative Conduits

Colon

Colon is a versatile conduit that can be used as an esophageal conduit for both malignant and benign disease. In adults, it is often used when stomach is unavailable due to previous operations, ulcers, or caustic burns. Reconstruction with colon is relatively common in children due to concerns of long-term complications with gastric transposition. A pedicled segment of left colon is most commonly used as it typically is of sufficient length the reach the neck, is of relatively small diameter, and has peristaltic ability.

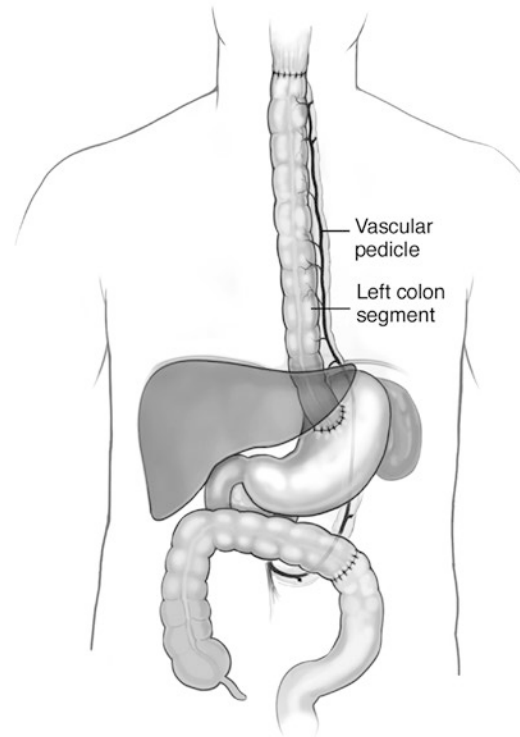

Fig. 55.2 Colonic interposition using pedicled left colon and a cervical anastomosis (Artwork by Marcia Williams)

An illustration of a colon interposition is shown in Fig. 55.2. The blood supply is maintained via an ascending branch of the left colic artery. In comparison, the right colon is shorter and larger in diameter, often lacks a marginal artery, and may be used when both the stomach and left colon are unavailable. The disadvantages of colon include the potential for leak of colonic contents in both the chest and abdomen, as well as the need for larger incisions for mobilization and the creation of three anastomoses. Patients with inadequate mesenteric blood supply due to atherosclerosis or an interrupted marginal artery or those with colonic disease are excluded as candidates. Over time the colon tends to dilate and lose tone and thus decline in function. In the long term, dilation and kinking can result in stasis and obstruction. Techniques to reduce dilation include minimizing conduit redundancy and eliminating sigmoid deformity at the time of the initial operation.

Jejunum

Jejunum is another option for esophageal replacement, particularly for distal esophageal resection or for replacement of the esophagus and stomach when malignancy involves both organs. Jejunum has been used as an intact loop, in a Roux-en-Y reconstruction, as an interposition between esophagus and stomach, and as a free tissue graft with use of microsurgical vascular anastomoses [10]. Advantages to the use of jejunum include the similarity of tube diameter to the esophagus, the ability of the graft to maintain peristalsis, and the ability to act as a barrier to reflux if of sufficient length. The use of jejunum is limited by the complexity of the mesenteric vessels. Obtaining a long segment of jejunum is often complicated by significant angulation and redundancy due to the tight radius of the blood supply. Careful dissection is necessary to prepare a long loop of jejunum that will reach the neck. To prepare the jejunal loop, the abdomen is typically opened via an upper midline incision and the small bowel is lifted out of the abdomen. The vascular anatomy of the small bowel is then inspected. In order for the jejunal loop to reach the neck, an average of four main jejunal branches from the superior mesenteric vessels need to be divided. Prior to division, bulldog clamps can be placed across the site of proposed transections to assess adequacy of the blood supply [19]. If mobilization creates excess intestine relative to the mesentery, redundancy can be overcome by excision and re-anastomosis of bowel [20, 21]. The jejunum can then be tunneled in an antecolic or retrocolic fashion, with antecolic reducing the risk of kinking of the vasculature. Figure 55.3 shows the tight

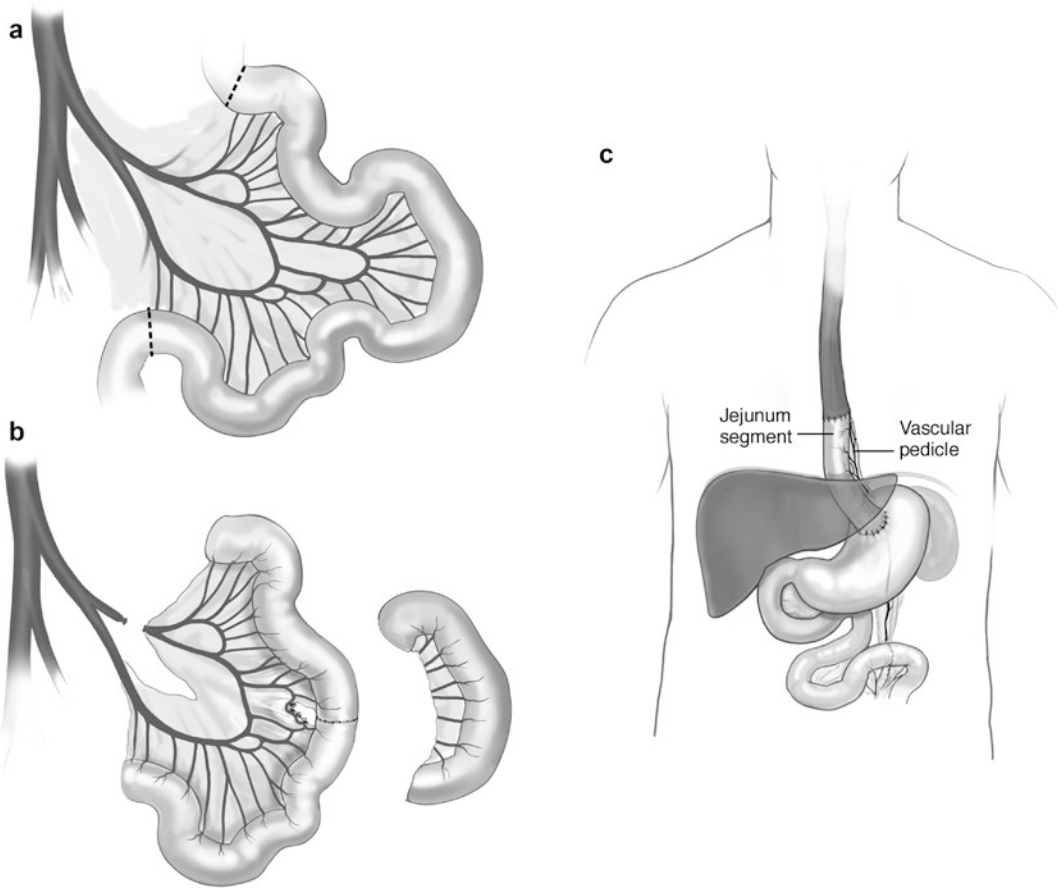

Fig. 55.3 Pedicled jejunal graft. (**a**) Illustrates the tight angulation of the jejunal vasculature, (**b**) excision of redundant bowel, and (**c**) anastomosis of the pedicled graft to the esophagus and stomach (Artwork by Marcia Williams)

angulation of the jejunal vasculature, excision of redundant bowel, and anastomosis of the pedicled graft to the esophagus. In patients with marginal vascular arcades, microvascular anastomosis of the internal mammary vessels has been used to augment blood supply [22].

Physiology of the Intrathoracic Stomach

The translocated stomach exists in an altered physiological environment. As described by Holscher, the blood supply is typically decreased by 10–20 % due to ligation of the left gastric and left gastroepiploic arteries [23]. Poor perfusion in the translocated stomach has been correlated with both increased rates of leak and stricture. Pierie et al. found that a reduction of perfusion below 70 % of pre-reconstruction values predicted anastomotic stricture formation [24]. Additionally, Ikeda et al. found that patients with low tissue blood flow by laser Doppler flowmetry were more likely to develop leaks than those with higher tissue blood flow [25].

Depending on the preparation of the stomach, the storage capacity and parietal cell mass are usually reduced due to partial resection of the fundus and corpus. The stomach's shape is changed by surgical manipulation and by stretching. Additionally, the transposed stomach is moved from the positive pressure environment in the abdomen to the negative pressure environment of the chest. In its new role as the neoesophagus, the usually receptive stomach is changed to a conduit of food and liquid boluses. A complete vagotomy permanently changes the stomach's innervation, as further discussed below. Gastric acid is at least temporarily decreased while gastrin levels are elevated [26].

The Vagal Nerve's Impact on Functional Outcomes

Many of the functional outcomes associated with esophageal reconstruction can be related to sectioning of the vagus nerve. The vagus broadly innervates structures in the head and neck, chest, and abdomen. Surgical division during resection and reconstruction of the esophagus results in predictable alterations to normal physiology. Injury or stretching of the vagus or the recurrent laryngeal nerve above the level of surgical division causes additional complications.

Anatomy of the Vagus Nerve

The vagus nerve exits the skull via the jugular foramen and descends within the carotid sheath into the mediastinum between the internal jugular vein and internal carotid artery. In the neck, the vagus branches to supply the larynx, pharynx, and heart. The superior laryngeal branch provides motor innervation to the cricothyroid muscle, which is responsible for control of vocal pitch. Pharyngeal branches provide motor innervation to all the muscles of the pharynx, with the exception of the stylopharyngeus muscle, and muscles of the palate except for the tensor veli palatini muscle. Cardiac branches descend into the mediastinum and provide parasympathetic innervation to the heart. The left and right vagi enter the mediastinum, where they give rise the recurrent laryngeal nerve (RLN) and divide into several branches around the esophagus. The recurrent laryngeal nerves run in the tracheoesophageal groves on both sides of the neck. The right recurrent nerve loops around the subclavian artery, while the left loops around the aortic arch. The RLN is main motor nerve of larynx. It also supplies the upper esophageal sphincter's cricopharyngeus muscle and thus plays a significant role in swallowing.

In the chest, the left and right vagal nerves descend parallel with the esophagus and form cardiac, pulmonary, and esophageal plexuses. The esophageal plexus forms between the level of the tracheal bifurcation and the level of the diaphragm. It is involved in motility of the esophagus and regulation of lower esophageal sphincter pressure [27]. The pulmonary vagal plexus is involved in pulmonary vasculature dilation and the cough reflex [28, 29]. Both left and right vagi contribute to parasympathetic innervation of the heart; however injury to the right, but not the left, increases heart rate via loss of attenuation of

activity of the sinoatrial node [30]. The esophageal plexus merges above the esophageal hiatus to form anterior (left) and posterior (right) vagal trunks that pass into the abdomen.

Once in the abdomen, each trunk separates into two divisions. The anterior trunk gives off the hepatic division that supplies the liver and gallbladder, with a branch reaching the pylorus and the duodenum. The anterior gastric division descends along lesser curvature of the stomach, giving branches to anterior gastric wall. The posterior trunk splits into the celiac division and posterior gastric division. The celiac division is the largest of the four divisions and leads to the celiac plexus, where it supplies parasympathetic fibers to the abdominal viscera [31].

Division of vagal branches to the fundus results in impairment of receptive relaxation, acceleration of gastric emptying of liquids, and decreased gastric acid production [32, 33]. Sectioning of the hepatic branch is associated with hypotonia of the gallbladder and the formation of gallstones [34, 35]. Division of the celiac branch is associated with impairment of motility and neuroendocrine disturbances [36, 37]. Multiple vagal branches supply the pylorus, with the hepatic plexus being most important [38]. An illustration of neck, chest, and abdominal vagal anatomy is shown in Fig. 55.4.

Vagal Injury During Esophageal Reconstruction and Its Consequences

In the neck, the recurrent laryngeal nerve is at risk of injury during circumferential dissection of the esophagus, if a cervical anastomosis is performed. During an extended resection with a formal lymph node dissection for cancer, the left RLN is additionally at risk during dissection of the aortopulmonary (AP) window lymph nodes or nodes along the left paratracheal groove. In this case, performing cervical incision on left reduces risk of bilateral RLN injury [39]. Recurrent laryngeal nerve injury results in vocal cord paralysis with hoarseness, impairment of coughing, swallowing and breathing, aspiration pneumonia, and, if bilateral, stridor and respiratory failure requiring reintubation or tracheostomy [39]. In a study of adults who underwent transhiatal esophagectomy for cancer, Hulscher reported a 22% rate of postoperative vocal cord paralysis and however found that this was permanent in only 4%. The authors concluded that most injuries were likely due to traction or stretching rather than transection [39].

Esophagectomy traditionally requires a truncal vagotomy with division of both the anterior and posterior vagal trunks. This results in loss of pyloric control of gastric emptying, gastric stasis, decreased gastric acid production, and dumping, as further described below [40–42]. An illustration of the abdominal vagal anatomy with truncal and highly selective vagotomy is shown in Fig. 55.4. A summary of consequences of vagal injury or division by location is shown in Table 55.1.

Alternatively, Akiyama et al. described the technique of a vagal-sparing esophagectomy for patients with benign disease or Barrett's esophagus with high-grade dysplasia. The vagi are identified and a limited, highly selective proximal gastric vagotomy is performed. The stomach is divided just below the GEJ, and the esophagus is inverted to remove the esophagus by invagination or eversion while preserving the esophageal plexus and the distal vagal trunks. The esophagus is then typically reconstructed with a colon interposition graft [43, 44]. Vagal-sparing esophagectomy has been shown to decrease dumping, diarrhea, and weight loss relative to transhiatal or en bloc esophagectomy in adult patients with high-grade dysplasia or intramucosal adenocarcinoma [45].

In total, the alterations introduced by placing the stomach in the chest, including division of the vagus nerve, affect gastric secretion, motility, gastric emptying, and gastroesophageal and duodenogastric reflux [23]. Many of the long- and short-term complications that occur after gastric pull-up are a direct consequence of these alterations. A summary of short- and long-term complications is shown in Table 55.2.

Perioperative and Short-Term Outcomes

In children, case series have established a 0–5.2% mortality rate for gastric transposition. The reported leak rate ranges from 12% to 36%.

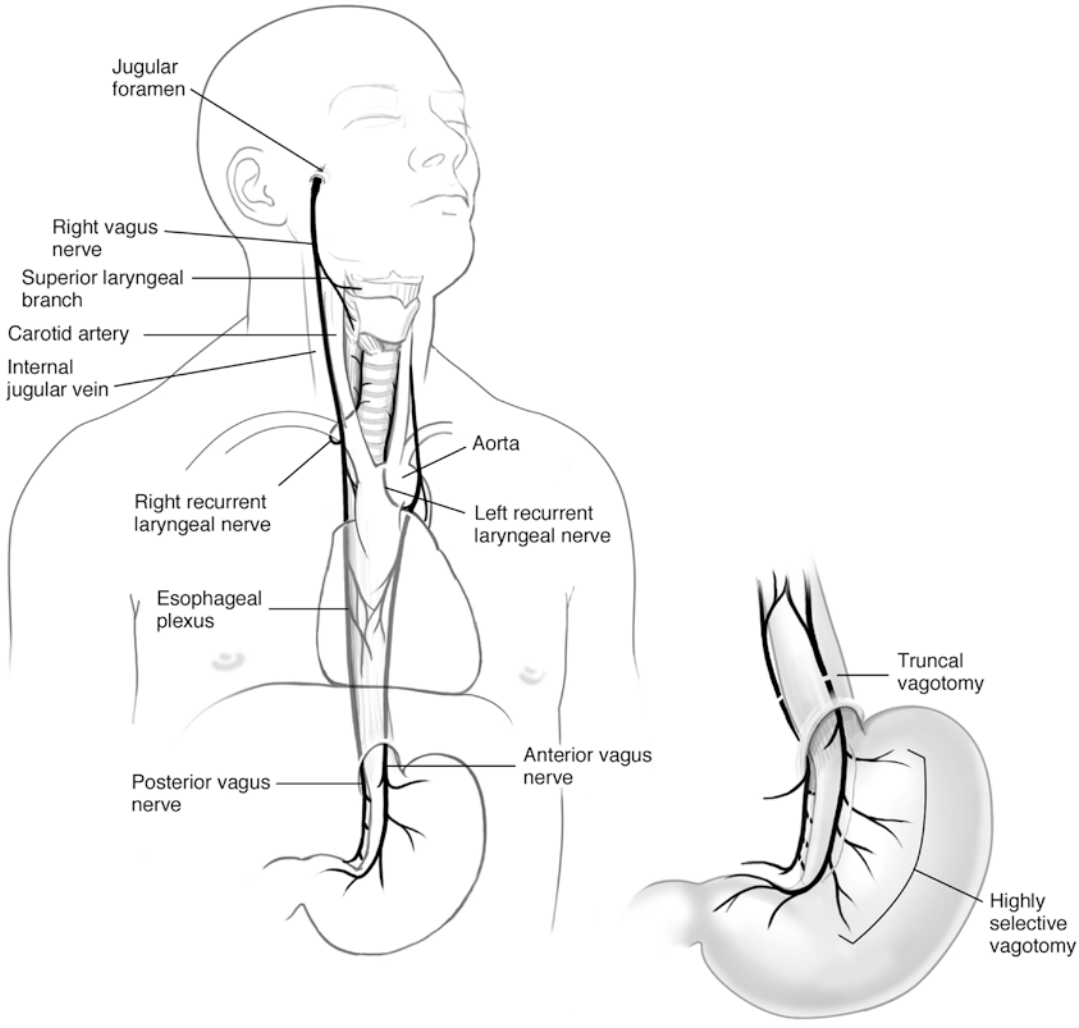

Fig. 55.4 Anatomy of the vagus nerve. *Inset* compares the divisions of a truncal vagotomy to those of a highly selective vagotomy (Artwork by Marcia Williams)

Table 55.1 Consequences of vagal nerve injury or division, by location

Location	Site of injury or division	Consequences of injury
Neck	Recurrent laryngeal nerve	Vocal cord paralysis with hoarseness, impairment of coughing, swallowing and breathing, stridor, respiratory failure requiring reintubation, aspiration pneumonia
Chest	Recurrent laryngeal nerve	Vocal cord paralysis as above
	Esophageal vagal plexus	Impairment of esophageal motility and LES pressure regulation
	Right cardiac vagus	Increase in heart rate via loss of attenuation of activity of the sinoatrial node
	Pulmonary vagal plexus	Impairment of pulmonary vascular dilation and the cough reflex
Abdomen	Hepatic/gallbladder branch	Hypotonia of gallbladder, increased rate of gallstone formation
	Gastric fundus branches	Acceleration of liquid emptying, impairment of receptive relaxation, and decreased gastric acid production
	Celiac branch	Impairment of bowel motility and neuroendocrine dysfunction
	Truncal vagotomy	Diarrhea, dumping, delayed gastric emptying

Table 55.2 Complications of gastric reconstruction of the esophagus

Short-term	Long-term
Leak	Decreased pulmonary function
Stricture (short- and long-term complication)	Dysphagia
Graft ischemia	Odynophagia
Graft loss	Weight loss/lack of weight gain
Vocal cord paralysis	Malnutrition
Chylothorax	Impaired gastric emptying
Aspiration	Dumping syndrome
Pneumonia	Anemia
Sepsis	Atrophic gastritis
Pulmonary embolus	Acid reflux
Death	Bile reflux
	Esophagitis
	Barrett's esophagus
	Esophageal stump dysplasia and cancer
	Diaphragmatic hernia
	Redundant conduit

Strictures formed in 19.6–49 % with one study approximating that 40 % of strictures formed in patients who were being treated for caustic ingestion. Other short-term complications include vocal cord paralysis, aspiration, chyle leak, effusions, and pneumonia [1, 4].

In comparison, series describing the outcomes of colonic transposition report a 0–4 % mortality rate, an 8–9 % rate of graft necrosis or ischemia, a 6–40 % leak rate, and a 28–50 % rate of anastomotic stricture [46, 47]. In 2007 Tannuri et al. published a comparison of esophagocoloplasty ($n = 115$, using transverse colon conduit with maintenance of a double blood supply via the left colic vessels and the marginal paracolic arcade via the sigmoid vessels) versus gastric transposition ($n = 34$) and found a 0.9 % mortality rate, 2.6 % major complication rate, and 85.2 % minor complication rate for esophagocolonoplasty versus a 5.9 % mortality rate, 23.5 % minor complication, and 52.9 % minor complication rate for gastric transposition [48]. The authors conclude that colon transposition is superior; however it should be noted that the two study groups were not comparable, with colon transposition representing the default operation.

In adults, overall mortality and survival have been similar between esophagectomy for cancer reconstructed with gastric transposition or colon; however some authors report higher morbidity for colonic transposition, with higher rates of anastomotic leaks and abdominal septic complications [49]. Reported 30-day mortality rates for esophagectomy with reconstruction for cancer range from 2.7 to 4.8 % and are not significantly different between colon and gastric interposition [49, 50]. Biel et al. reported that prevalence of endoscopically detected graft ischemia was similar with gastric and colonic reconstructions: 10.4 % versus 7.4 %, respectively. The prevalence of strictures was more common and more severe after gastric than colonic reconstruction [50]. At our institution, utilizing a three-incision esophagectomy technique with cervical esophagogastrostomy, the 30-day mortality for esophageal carcinoma patients is 3.6 % with a median survival of 25 months. Overall 3-year survival was 44 %. Recurrent laryngeal nerve injury occurred in 14 %, chylothorax in 9 %, and leak in 8 % [51].

Series reporting experience with jejunal interposition for esophageal replacement in patients of all ages found a 0–3.5 % mortality rate, 5–10 % leak rate, and 0–5 % rate of graft loss [52–54].

Long-Term Function and Complications

Studies of long-term functional outcomes in adults have been limited by the low survival rate of esophageal cancer; however there are multiple recent studies that illuminate the function and complications of esophageal replacement years after esophagectomy and reconstruction. In children, long-term results are obtained from published small case series. Regardless of the age of the patient, the published literature focuses on quality of life, swallowing function, gastric emptying and its consequences, nutrition status, and the long-term consequences of bile and acid reflux, as discussed below. Less reported findings

of impairment in pulmonary function and uncommon complications such as diaphragmatic hernia or redundant conduit are also discussed.

Quality of Life

There are limited numbers of studies comparing quality of life after reconstructions with different types of conduit. In children, quality of life was found to be generally unimpaired for patients who had gastric transposition for esophageal atresia, although the patients tended to be less socially and emotionally independent than their peers [55]. In adults at least 5 years after esophagectomy for cancer, physical function and level of energy SF-36 scores were significantly decreased from the national average; however the ability to work, social interaction, daily activities, emotional dysfunction scores, and perception of health were similar to national norms. Patients had significantly higher scores in mental health [56]. In patients who underwent esophageal reconstruction for benign disease (71.6% with stomach, 19.8% colon, and 9.6% small bowel), physical functioning, health perception, and social functioning were decreased compared to national norms a median of 9.8 years after surgery. Bodily pain, ability to work, energy level, emotional problem, and depression scores were similar to national norms [57].

Swallowing/Dysphagia

In a study of long-term effects of gastric transposition in children at least 5 years after surgery, Davenport et al. reported that 94% of patients had a normal, unmodified diet; however only 29% had asymptomatic swallowing [11]. Many children were noted to have developed a coping mechanism of drinking copious water when eating. In his series, Spitz et al. found that 30.6% had early postoperative swallowing problems, which persisted in half [4].

In a study of adults who were also at least 5 years after esophagectomy (93% with gastric reconstruction), 25% of 107 patients reported dysphagia to solid food and 9% had pain on swallowing. Nine percent reported dysphagia to pureed diet and 3% had dysphagia to liquids. Thirty-seven percent stated that they altered their food intake to eat smaller more frequent meals. Forty-three percent of these patients had undergone at least one postoperative dilation [56].

Gastric Emptying

Although the intrathoracic stomach (whole or gastric tube) is commonly thought to act as an inert tube after esophagectomy, with food emptying only by gravity, motor activity of the denervated stomach slowly recovers with time [58, 59]. Furthermore, motor recovery may be better in whole stomach transpositions relative to gastric tubes [60]. Accordingly, studies of gastric emptying tend to show improvement over time. In adults, Lee et al. found that 50% of patients had markedly prolonged gastric emptying of solid foods immediately after esophagectomy; however gastric emptying improved and the further patients were out from their operation [61]. Urshel et al. reported that pyloric drainage (pyloroplasty) reduced the occurrence of early postoperative gastric outlet obstruction and however had little effect on other early or late patient outcomes such as gastric emptying, nutritional status, or bile reflux [62]. Similarly, a study of children at least 5 years out from gastric transposition found that in 82%, more than 50% of solid and liquid contents left the stomach by the time of meal completion (5 min) [11].

Dumping

Dumping syndrome is a group of symptoms that result from rapid gastric emptying, including diarrhea, palpitations, pallor, abdominal cramps, weakness, sweating, dizziness, or the need to lie down after eating. Delivery of a large bolus of hyperosmolar contents to the duodenum causes a fluid shift from the intravascular compartment to the intestinal lumen, resulting in a decrease in circulating volume [63]. Increased release of several gastrointestinal hormones may also play a role. Late dumping symptoms that occur 1–3 h

after a meal are attributed to reactive hypoglycemia [64]. In children, Davenport et al. found that 12 % of children experienced postprandial weakness and dizziness. Twenty-three had significant episodes of diarrhea "at least once a week," precipitated by consumption of sweets, yogurt, or sugary foods. Interestingly, no correlation was found between the presence of diarrhea and dumping and radionuclide gastric emptying [11].

In adults 5 or more years after surgery, 50 % reported experiencing symptoms of postprandial dumping, including 24 % with diarrhea, 16 % with cramps, 8 % with nausea, 7 % with dizziness, and 6 % with diaphoresis [56]. In a comparison of symptoms in adults after vagal-sparing esophagectomy with colonic interposition, standard esophagectomy with colonic interposition and esophagectomy with gastric pull-up, Banki et al. found dumping symptoms in 1 of 15 (7 %), 3 out of 10 patients (30 %), and in 1 out of 10 (10 %), respectively [44]. In larger series, rates of dumping after gastric pull-up have been reported at 18–50 % [56, 65, 66] and typically decline with time [67]. Furthermore, Headrick et al. found that patients with a cervical anastomosis were more likely to have dumping symptoms relative to those with an intrathoracic anastomosis [68], possibly due to interruption of vagal fibers in the high thorax.

Feeding Intolerance

Feeding intolerance can result from lack of gastric emptying, pain with swallowing, strictures, or dumping symptoms. In a report of 42 children who underwent gastric transposition for esophageal reconstruction, 20 % had feeding tolerance necessitating jejunal feeds at a mean follow-up of 6.5 years, due to delayed gastric emptying in three, severe neurological impairment in four, and feeding aversion from esophageal atresia in one [1]. Prolonged jejunal feeding in adults is rarely reported.

Weight Gain/Loss

In children, restrictions in weight gain may result as both a result of other congenital anomalies or as a complication of esophageal reconstruction. At least 5 years after esophageal reconstruction for esophageal atresia, caustic ingestion or reflux, Davenport et al. found that only 65 % of children were above the third percentile of weight, and 76 % were above third percentile of height [11]. Similarly, Hirschl found that 40 % of children status post reconstruction with gastric pull-up for esophageal atresia were below the fifth percentile in weight [1].

In adults, most of whom undergo esophagectomy for malignant disease, maintenance of weight is related both to the function of their reconstruction and the status of their underlying disease. In a study of cancer patients at least 5 years after esophagectomy, Mclarty et al. found that 49 % never regained lost weight after the operation, 25 % maintained initial preoperative weight, and only 6 % gained weight [56]. In patients who underwent esophagectomy for high-grade dysplasia, assessment of those alive 2 years or more after surgery, 65 % had lost weight, 21 % had no change in weight, and 14 % had gained weight [68]. In contrast, a study of patients who underwent esophagectomy with gastric reconstruction for achalasia at a median follow-up of 43 months, postoperative weight was similar to optimized preoperative weight in men and women and did not change significantly with time [69].

Anemia

Iron absorption is facilitated by the presence of acid in the stomach, which aids in the conversion of ferric iron to ferrous iron and assists in the chelation of ascorbic acid for absorption in the duodenum. Truncal vagotomy results in loss of acetylcholine stimulation for gastric acid production. Correspondingly, basal and maximal gastric acid production is markedly decreased in most intrathoracic stomach patients, with associated elevations in serum gastrin [23, 36, 70]. The denervated stomach is able to recover intraluminal acidity over time; however [71] Tagami found that absorption of vitamin B_{12} is decreased immediately after esophagectomy but recovers after

about 1.5 years after operation [72, 73]. This transient decline in absorption has been found to be due to decreased excretion of intrinsic factor from parietal cells of the stomach [74].

In children at least 5 years after surgery, 33 % were found to be anemic, 47 % were found to have low mean corpuscular hemoglobin, and all patients tested had low serum ferritin, consistent with iron deficiency anemia. There was no evidence of B_{12} deficiency [11]. In adults, similar rates of anemia have not been found [23].

Atrophic Gastritis

Atrophic gastritis is found in 40–75 % of adult patients with an intrathoracic stomach [23, 26, 70, 75]. In addition to the histological changes induced by vagal sectioning, Okada et al. hypothesized that the high rates of postoperative gastritis may be due to the advanced age of most esophagectomy patients and the reduction of blood flow of the stomach [26]. Chronic proton pump inhibitor (PPI) use could also contribute to the high rates of postoperative atrophic gastritis. In non-esophageal replacement patients (without division of the vagus nerve), an increase in the rate of gastric body atrophic gastritis has been reported with proton pump inhibitor and H2 receptor antagonist therapy [76, 77]. There is no documentation, however, that long-term pharmacologic or surgical acid suppression produces the multifocal atrophic gastritis with the extensive intestinal metaplasia that is associated with increased risk of gastric adenocarcinoma [78, 79]. Rates of atrophic gastritis may also be confounded by *H. pylori* infection. A cohort study showed that patients with *H. pylori* treated with omeprazole were at increased risk of atrophic gastritis, and this was confirmed in a randomized trial with long-term follow-up [80, 81]. In the studies of esophageal replacement patients, the *H. pylori* infection rate and PPI use have not been reported. Multiple investigators have found no association between the extent of duodenogastric reflux and degree of gastritis [23, 75]. Similar endoscopic studies with children have not been published.

Bile Reflux

Up to 60–80 % of patients after esophagectomy experience symptoms of reflux and symptoms may originate from reflux of either bile or acid. Symptoms include regurgitation, heartburn, dysphagia, inability to lie flat, nocturnal cough, and nocturnal aspiration. The pressure gradient between the abdomen and the thorax promotes reflux of duodenal contents into the gastric conduit and across the diaphragm [82]. Furthermore, truncal vagotomy impairs the propulsive activity of the antrum [32, 71]. While pyloric drainage improves gastric emptying and therefore reduces acid reflux, pyloroplasty may facilitate reflux of duodenal contents. Notably, investigators have found intragastric bile regardless of whether a pyloroplasty was performed. Symptoms, however, were not correlated to intrathoracic bile concentrations [83]. Bile salts injure both the gastric and esophageal mucosa and their effects are increased in the presence of gastric secretions [84]. In a study of patients who underwent Ivor-Lewis esophagectomy with gastric tube esophagogastrostomy and digital dilation of the pyloric ring, 44 % of patients were found to have reflux of bile. Symptoms of reflux did not correlate with reflux esophagitis; however there was a correlation between acid or bile reflux and endoscopic esophagitis [85]. Patients with pyloric drainage had more reflux esophagitis [86].

Acid Reflux, Barrett's Esophagus, and Malignancy in the Esophageal Stump

Esophageal reconstruction with esophagogastrostomy causes disruption of the body's normal anti-reflux mechanisms. The gastroesophageal junction (GEJ) moves into the chest, the esophagogastric anastomosis lacks the valve-like activity of the native GEJ, sectioning of the vagus impairs the motility of the esophagus and stomach, and traditional surgical anti-reflux procedures are not an option. As previously mentioned, 60–80 % of patients after esophagectomy report symptoms of reflux [82]. Reflux not only causes

Table 55.3 Endoscopic findings after esophagectomy and gastric pull-up in 101 advanced achalasia patients

	1 year (%)	5 years (%)	5–10 years (%)	>10 years (%)
Normal	53.6	41.6	23.0	29.9
Esophagitis	45.9	71.9	–	70.0
Gastritis	20.4	31.1	–	40.0
Columnar epithelium	0	109	29.5	57.5

Adapted from Rocha et al. [97]

symptoms but over time results in esophagitis, metaplasia, dysplasia, and carcinoma in the remnant esophagus. Barrett's esophagus occurs when damage to the squamous esophageal epithelium results in development of columnar metaplasia or potentially premalignant specialized intestinal metaplasia [87]. While the exact molecular events that effect this transformation are unclear, studies suggest a pathogenic role for *Cdx2* genes [88]. These genes are known to mediate the differentiation of intestinal epithelial cells and are not normally expressed in the esophagus and stomach. In mice, intestinal metaplasia could be induced by forcing gastric epithelial cells to express *Cdx2*. In humans, 100 % of biopsy specimens with Barrett's specialized intestinal metaplasia stained positive for *Cdx2* [89]. The continued molecular changes involved in the evolution from Barrett's metaplasia to adenocarcinoma are also poorly understood; however genetic analyses revealed chromosomal losses and gains, as well as gene amplifications [90–92]. In patients who do not have a history or esophageal reconstruction, the risk of progression of Barrett's metaplasia to dysplasia and cancer is between 0.2 and 2.9 % per year [93, 94].

The American College of Gastroenterology recommends that patients with Barrett's esophagus without dysplasia undergo surveillance endoscopy every 3 years. Those with low-grade dysplasia are recommended to undergo endoscopy annually. Patients with high-grade dysplasia should undergo endoscopy every 3 months and be considered for esophageal resection [95].

In endoscopy studies of adult patients after esophagectomy with whole stomach or gastric tube reconstruction, rates of esophagitis ranged from 30 % to over 70 % [84, 96, 97]. As determined by Rocha et al. rates of esophagitis increase with time since surgery. In his study of patients who had undergone esophagectomy with cervical esophagogastrostomy for achalasia, the incidence of esophagitis in the esophageal stump was 45.9 % at 1 year, 71.9 % at 5 years, and 70.0 % at 10 years follow-up. Furthermore, the occurrence of ectopic columnar metaplasia and Barrett's esophagus in the esophageal stump was none before year 1, 10.9 % between years 1 and 5, 29.5 % between years 5 and 10, and 57.5 % at 10 or more years follow-up. H_2 blockers and proton pump inhibitors did not avoid the occurrence of Barrett's esophagus; however there was a tendency for medical acid blockers to delay the appearance and size of columnar epithelium. Of the patients with intestinal metaplasia, 2 of 23 (8.7 %) developed high-grade dysplasia 13 and 19 years after their initial operation. In both patients, this later developed into in situ adenocarcinoma 1 and 3 years after the diagnosis of dysplasia. Of patients followed for more than 5 years, 5 of 61 patients (8 %) developed cancer of the esophageal stump. Three patients developed squamous cell carcinoma and two patients developed adenocarcinoma. These later two patients developed cancer 22 and 34 years after their initial operation [84]. A table summarizing Rocha et al.'s endoscopic findings is shown in Table 55.3. Similarly, in a study of 48 adult patients who underwent esophagectomy with esophagogastrostomy primarily for cancer, O'Riordan et al. reported a 50 % incidence of columnar metaplasia above the anastomosis at a median 26 months post surgery. Of these patients, specialized intestinal metaplasia was detected in 54 %. The magnitude of acid or bile reflux was not found to be related to the prevalence of metaplasia; however duration of reflux was significantly correlated [98].

In children, a study of 14 patients who had undergone gastric tube reconstructions most commonly for esophageal atresia, 10 patients (71 %) were found to have Barrett's esophagus on endoscopy at least 2 years after surgery. There was no intestinal metaplasia or dysplasia found. Clinical symptoms were a poor indicator of cervical esophageal pathology [99]. Adenocarcinoma has been reported in a patient 20 years after esophageal atresia repair [100].

Pulmonary Function

Davenport et al. reported the respiratory symptoms and pulmonary function of children at least 5 years after gastric transposition. Forty-one percent had no respiratory symptoms, such as episodes of breathlessness or tiredness; however 94 % had lung function indexes below predicted values for height. The median total lung capacity (TLC) was 68 %, and forced vital capacity (FVC) was 64 %; however the ratio of forced expiratory volume in 1 s to FVC (FEV1 to FVC) was normal, indicating normal airway resistance. There was no correlation between PFT results and reported respiratory symptoms. Many of these children had undergone multiple thoracotomies [11].

In adults, it is unclear if this decrease in pulmonary function is present. In patients who underwent pulmonary function tests 6 months after thoracoabdominal esophagectomy with esophagogastrostomy, only vital capacity and total lung capacity were significantly reduced after the operation, however not to a clinically relevant degree [101].

Diaphragmatic Hernia

Diaphragmatic hernia is a rare complication after esophagectomy. In a review of 1,075 esophagectomies over a 12-year period using either whole stomach or gastric tube conduit, Kent et al. estimated that the incidence of a diaphragmatic hernia was 2.8 % for minimally invasive esophagectomy and 0.8 % after open esophagectomy. The mean time to diagnosis was 32 months post esophagectomy. In 17 % this herniation was asymptomatic. Abdominal pain was present in 45 %, dyspnea in 15 %, and dysphagia in 15 % and nausea and constipation in 10 % each. Colon was the most commonly herniated organ. Operative repair was necessary in most patients [102].

Redundant Conduit

Kent et al. also determined the incidence of another rare complication after esophagectomy. The authors reported a 3.6 % incidence of redundant conduit after minimally invasive esophagectomy with gastric tube reconstruction with pyloroplasty. One patient (<1 %) developed redundant conduit after open transhiatal esophagectomy. Dysphagia (43 %) was the most common symptom, followed by regurgitation (30 %), reflux (26 %), vomiting (22 %), aspiration (22 %), and early satiety (9 %). The cause of redundant conduit was determined to be excess conduit left above the diaphragm at time of esophagectomy in 23 %, mechanical obstruction to emptying in 54 % (such as lack of drainage procedure, pyloric stricture, or a too small hiatal aperture), twisted conduit in 14 %, and no anatomical basis identified in 9 %. Revisional surgery was performed in all but one patient [102].

Conclusions

There are advantages and disadvantages with all conduit options for esophageal reconstruction, and there is no clear best choice for all patients. Stomach is commonly used because of the relative ease of operation and reduced operative times. Use of stomach for esophageal reconstruction can be performed with minimal perioperative morbidity and mortality. While long-term functional results and quality of life are satisfactory, the problem of duodenal and gastric reflux predisposes gastric reconstruction patients to strictures, esophagitis, Barrett's esophagus, and cancer of the esophageal stump. The high reported rate of endoscopic abnormalities indicates the need for regular endoscopic surveillance of patients after gastric transposition. In children

and young patients with benign disease, surgeons and patients should weigh the long-term risks associated with gastric reconstruction and consider the use of alternative esophageal conduits.

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Late Follow-Up of Colon Interpositions

56

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Introduction

Children with long-gap esophageal atresia who are otherwise healthy may have a normal life expectancy. Therefore, durability and function of an esophageal substitute is essential. Long-term follow-up is critical as problems may present decades after the original surgery.

There are several methods for bridging a gap of esophagus. These include (1) a reversed gastric tube, (2) bringing the stomach into the chest or neck, (3) a jejunal conduit, (4) using the right colon based on the middle colic pedicle, (5) using the transverse colon based on the left colic pedicle in isoperistaltic fashion, and (6) using the descending colon based on the left colic pedicle placed antiperistaltically.

Construction of an esophagus from an interposed segment of colon was first described by Lundblad in 1921 [1]. In 1955 Dale and Sherman described a retrosternal colonic interposition [2]. Waterston popularized the posterior mediastinal transthoracic approach in 1957 [3]. Many modifications have been introduced in efforts to promote normal function with great variation in both early and late morbidity and mortality.

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Hendren and most other authors prefer the method described by Waterston for several reasons. It is more versatile than a substernal conduit which must reach the neck. The Waterston operation allows substitution of only that length of esophagus which is abnormal or absent. As these conduits empty principally by gravity, there does not seem to be significant functional differences between an isoperistaltic and an antiperistaltic segment [4]. The Waterston approach may be through a left thoracoabdominal incision although a transhiatal approach is also reported in large series [5, 6].

This current chapter recognizes the diversity of surgical approaches to colon interposition and that these approaches will not necessarily have identical results. Often, diverse approaches are included in case series. For example, Hendren's series of 32 patients included 28 having a left thoracoabdominal approach, with a transverse colon isoperistaltic graft typically based on the blood supply of the left branch of the middle colic. The lower anastomosis was performed in 24 patients into the stomach with 7 into the anterior wall and in 17 into the back wall. Most (28 of 32), but not all, had a pyloroplasty performed either previously ($N=3$) or at the time of colon interposition. Bassoinny used an isoperistaltic left colon graft with pyloroplasty in all, while Burgos used this approach in the majority with routine pyloroplasty [6, 7]. Kelly used mostly retrosternal grafts, while Lindhahl used both retrosternal and

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intrathoracic grafts without a significant difference in complications [8, 9].

The timing of colon interposition should also be mentioned. Hendren reported the performance of a colon interposition in the first year of life, as shown by seven cases in his series [5]. However, he and others believe the operation should not be performed in the newborn, as the blood vessels are very small and the colon is quite small, especially in cases of pure esophageal atresia without tracheoesophageal fistula which would be the principal indication for consideration in the newborn period. As emphasized by others, it may give a slightly added margin of safety to wait until the patient is between age 1 and 2 years, since this is a formidable operative procedure.

Indications

The indications for esophageal replacement in children are typically from complicated or long-gap esophageal atresia, corrosive damage from caustic ingestion, or from severe gastroesophageal reflux disease. Hendren's series over 25 years notes the indications for operation to include 21, esophageal atresia; 5, caustic injury; 3, peptic stricture; 2, esophageal varices with previous splenectomy; and 1, cartilaginous hamartoma of the esophagus. There were six secondary cases (all done elsewhere and were referred for revision): three failed gastric tube with peptic esophagitis, bleeding, stenosis, and recurrent aspiration; one presternal jejunal conduit; one failed/sloughed colon esophageal interposition with transverse colon; and one extensive stenosis after primary repair of esophageal atresia as an infant [5]. This series which now includes 62 patients is being updated.

Other series report heterogeneity which may limit broad application. Ahmad's series includes 38 total patients: 24 with esophageal atresia repaired at a mean age of 17 months and 14 with caustic strictures repaired at a mean age of 7.4 years [10]. Coopman reported 17 esophageal atresia patients and 15 with corrosive strictures [11]. West reported 31 patients total with esophageal atresia in 23, caustic ingestion in 6, and acquired stricture in 2 with a follow-up of 1–15 years [8]. Kelly reported 23 total with esophageal atresia in 9 and caustic ingestion in 14 with a 12.8-year follow-up. Burgos had 65 total patients with 30 esophageal atresia and 32 caustic ingestions, and Khan had 25 patients with esophageal atresia in 23 and corrosive strictures in 2 [7, 12].

Three authors report series of exclusively caustic ingestion patients. Canty provides a series of 7 [13]. Bassiouny reported an initial 70 children in 1992 who were followed 6 months to 5 years, which was later updated in 2002 to 100 patients, of whom 60 have been followed 5–15 years, all undergoing a transhiatal approach at a mean age of 3.4 years. Lastly, Hendren reported an additional seven patients with caustic strictures to the pharynx [14].

Only one series reported exclusively esophageal atresia patients of whom 20 underwent a colonic interposition out of 34 total [9].

Long-Term Follow-Up

Length of follow-up is also crucial to interpretation of these reports as complications may manifest decades after the original operation. Waterston was the first to provide long-term follow-up in 14 of his patients in 1976 over a 12-year period [3]. Hendren's report in 1985 included cases from 1959 to 1984 and provided an average 15-year follow-up with 20 of the patients ranging from 12 to 25 years [5]. His experience since then totals 62 cases. The inclusion of the more recent cases in need of long-term follow-up will be reported in the near future. Interpretation of case series must take this into account as length of long-term follow-up into account as this ranges from 3 to 33 years [7, 8, 10–12, 15–17].

Complications

Late Complications

The incidence of late complications, defined as those occurring after the first year, is substantive and tends to be more frequent in those with

esophageal atresia versus other indications for colonic interposition [11]. There is a broad range of complication rates related to the definition, occurrence, and the intensity of scrutiny. Approximately 25 % undergo repeat surgical intervention [7].

Graft Failure

The ultimate survival and function of the original colon conduit with excellent function and durability is critical to the long-term satisfaction of adults who may live with their graft for 70+ years. Several authors report no graft loss in their long-term series [5, 13, 17, 18]. Waterston's original series reports one graft failure, with other series reporting graft failure rates of 3–18 % [19]. Burgos reports 2 of 65 which had significant dilation of the graft requiring replacement, while Khan reports one of 25 [7, 12]. Ahmad's series reported 18 % who required graft replacement due to various causes such as graft redundancy, tracheocolonic fistula, cervical anastomotic breakdown, and severe graft ulceration with bleeding. Graft perforation due to ischemia is a rare event [10].

Graft Redundancy

The placement of a colonic interposition, typically in infants or toddlers, is expected to grow "with the child" and serve as a passive conduit for the passage of food throughout life. There are reports of isoperistaltic sequential or propulsive waves promoting evacuation of the graft contents and the clearance of refluxed gastric fluid suggesting retention of some level of intrinsic colonic motility. However, most show that these contractions are ineffectual and the colon empties by gravity, or the so-called "cascade" effect.

Colonic interposition grafts are prone to both dilation and elongation of the conduit over time, which can create difficulties and lead to revisions and/or graft replacement if symptomatic (see Fig. 56.1). Several theories exist to explain this phenomenon, some intrinsic to the growth pattern of the colon, while some implicate a relative

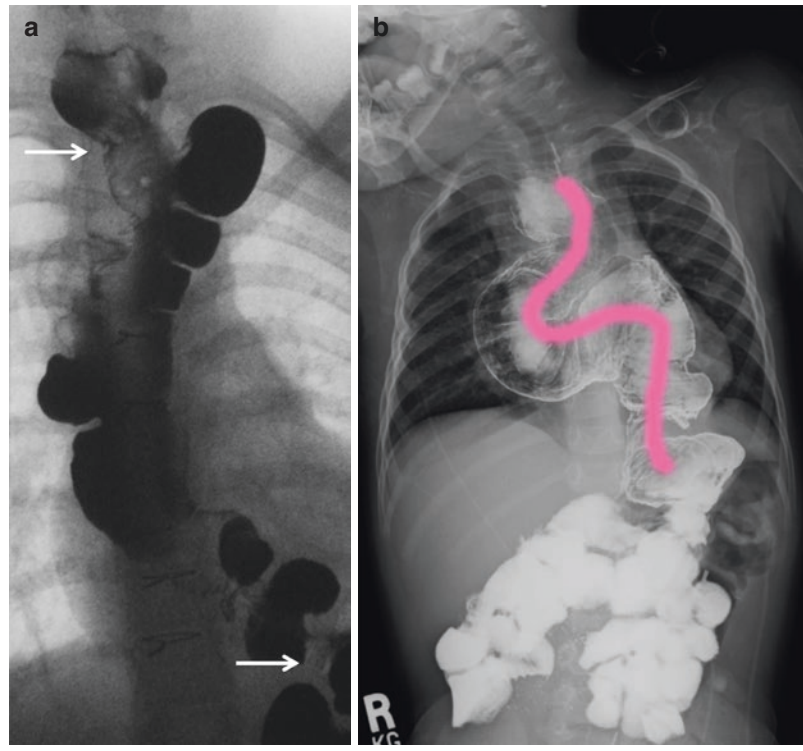

Fig. 56.1 (**a**) Normal "esophagram." Transverse colon with upper anastomosis in neck and lower anastomosis into back of stomach (*arrows*). Note satisfactory size of conduit and its straight course from neck via left pleural space to stomach. (**b**) Dilated colonic interposition years after the original surgery (Revision by partial resection of redundancy was ultimately required)

or acquired outlet resistance at the cologastric anastomosis as causative. Passive dilation may also occur above points of partial obstruction such as the thoracic inlet, main bronchus, diaphragmatic hiatus, or adhesions.

Overall rates of graft redundancy are typically 4–5 % in most series, but there are varied reports ranging from 0 % to 100 % as some authors report all radiographic dilation and others only report those whose symptoms require reoperation [12]. Canty reports no graft redundancy on contrast upper gastrointestinal studies in his seven patients although the follow-up is only modest at 2–7 years [13]. Lindhahl studied 14 of his patients with "esophagrams" noting the width of the colon was normal in 8 (57 %), dilated in 4 (29 %), and very dilated in 2 (14 %) with tortuosity in 3 [9].

Coopman reports a 17 % rate of dilation [11]. Conversely, Rode noted that all 16 of his patients had varying degrees of tortuosity of the interposed colon which was most marked distally. There was no spontaneous peristaltic movement seen under fluoroscopy, and the gastroesophageal junction was normal in all [16]. Others report more moderate rates of dilation. Of the 18 patients have contrast studies, Kelly noted that 4 (22 %) had redundancy, but only 1 was symptomatic [8].

Burgos noted 8 of 53 cervical redundancy of the graft in 8 of 53 patients which was a source of social embarrassment [8]. Six had episodes food impaction with several requiring endoscopic foreign body removal. He noted this was seen less with the transhiatal and retromediastinal location of the interposition.

Hendren reports 4 of 32 whose colon segment became redundant over years, causing partial functional obstruction (see Fig. 56.1b) [5]. This was remedied by shortening the lower bowel segment and altering its hiatus through the diaphragm to correct angulation as it passed from the thoracic gutter through the diaphragm to shorten and straighten the segments. He recommends that it is important to avoid redundancy and angulation in these colon segments as it can lead to functional obstruction [4, 5, 8]. The safest approach to shortening a conduit is at the cologastric anastomosis, dissecting along the bowel wall to avoid injury to the vasculature [5, 20].

Erdogan reports 4 of 15 patients who did not have an initial pyloroplasty who developed later graft redundancy (26.6 %) [15]. Only one required reoperation which resulted in a late mortality due to a leak. Ahmad noted an 11 % redundancy rate with all requiring revision due to severe redundancy which altered the vascular arcade; three had total graft replacement and one partial resection [10].

There are several authors whose series support the premise that symptomatic graft redundancy may take several decades to manifest. Domreis reports four patients with an average age of 37 years who developed symptomatic graft redundancy, an average of 16 years postoperatively [21]. Redundancy presented as dysphagia, regurgitation, pneumonia, or chest pain, and symptoms were improved after segmental resection. Dhir reports several patients with redundancy with an accompanying, and possibly causative, distal anastomotic stricture who underwent operative correction more than 20 years after their original surgery [22]. Basiounny noted minor increases in the occurrence of graft redundancy in his update reports, but none caused marked feeding problems [6, 18]. It should be noted these series have diverse patient populations and that those undergoing esophageal replacement at a later age due to corrosive ingestions may have a slightly favorable outcome.

Colonic Bacterial Overgrowth

The occurrence of bacterial overgrowth in the colonic conduit is rarely mentioned, with an incidence of 17 % noted by Coopman (2 of 17 patients) [11]. This is a potential source of malabsorption, so it should be considered in select patients.

Bezoars

The occurrence of bezoars is uncommon with only two series reporting this entity. Coopman noted the occurrence in 4 of 17, and Lindhal

noted that 2 of 15 required operative treatment for foreign body occlusion [9, 11].

Gastroesophageal Reflux

The occurrence of symptomatic "gastroesophageal" reflux (GER), or perhaps more correctly termed "gastrocolonic" reflux, is hypothesized to occur less frequently in colonic versus gastric interpositions as mucus production by the colon may be protective. The use of a pyloroplasty seems to be protective as Rode noted gastroesophageal reflux in four of seven (57%) without a pyloroplasty and in only 11% (one of nine) with a pyloroplasty [16]. Erdogan does not utilize a pyloroplasty and reports gastroesophageal reflux in 3 of 15 (20%). However, the absence of clinical symptoms and gastrointestinal hemorrhage in his cohort has lead him to suggest no pyloroplasty is needed [15].

In Hendren's series of 32 patients, 4 had symptomatic gastroesophageal reflux (12.5%). When reflux is seen on GI series, most patients are noted to have peptic distress, whereas asymptomatic patients do not seem to have significant reflux on contrast studies. Three pH testing and endoscopic biopsy showed alkaline gastritis which responded to medical therapy. Symptoms occurred in these patients 8, 10, 18, and 22 years postoperatively. One of the patients, now an adult, has nocturnal symptoms that suggest chronic aspiration pneumonitis.

Hendren noted the location of the anastomosis did not have a significant effect on the rate of reflux. GER occurred with the lower anastomosis into the rudimentary esophagus (12%), into the posterior stomach (12%), and to the anterior stomach (14%) [5].

Some authors report no gastroesophageal reflux [18]. Some have added an antireflux wrap in efforts to reduce GER. Vasseur Maurer evaluated patients with an esophagram with a reduction in GER from 48% down to 7.5% when a wrap was utilized. No difference in stasis within the graft was noted [23]. Canty reports a series of patients who had a Thal fundoplication who notes radiographic reflux into the conduit located within the abdomen, but no reflux above the diaphragm. All were asymptomatic.

Domreis reports severe late bile reflux in three which led him to convert the distal anastomosis into a Roux-en-y colojejunostomy combined with variable gastric resection [21].

Delayed Gastric Emptying

As emphasized by most authors, pyloroplasty appears to be an important adjunct in the performance of a colonic interposition [4–6, 13, 19, 24, 25]. As the integrity of the vagal nerves cannot be assured, pyloroplasty promotes gastric emptying and minimizes gastric reflux. Delayed gastric emptying is rarely reported. However, three patients who had pyloroplasty manifested alkaline gastritis many years later [17]. Further investigation of patients with peptic symptoms after colon esophageal replacement may uncover additional cases and screening is encouraged.

Dumping

Despite the common practice of performing a pyloroplasty during a colonic interposition, most authors provide no commentary on the occurrence of the gastric dumping syndrome. An incidence of 5% is noted by Ahmad (2 of 38) and 17% by Coopman (2 of 17) [10, 11]. Rode, however, reports normal gastric emptying on fluoroscopy in all [16]. Nuclear medicine gastric emptying studies are either not obtained or reported by most authors of large series.

Anastomotic Stricture

The occurrence of strictures at the proximal or distal interposition anastomosis is common, with up to 20% of all patients requiring surgical revision. Contributing mechanical factors must be considered such as compression at the clavicle or diaphragmatic hiatus.

Proximal strictures in the cervical esophagus are the more common and may manifest as

regurgitation of undigested food during meals or when recumbent. Reported occurrence rates vary from 4 to 28 % [7, 8, 10, 12, 15, 16, 18, 19]. Hendren reports one late anastomotic stricture at the proximal anastomosis which responded to steroid injection and cautious dilatation [5].

Many authors have noted that late strictures occur most frequently after initial leak or infection. A trial of dilation is warranted, with consideration of adjunctive steroid injection [5]. However, most authors report that ultimately one-third to one half of those with proximal strictures require late surgical revision at the cervical anastomosis [7, 10, 12, 16–19].

Distal strictures are diagnosed less frequently but may contribute to graft redundancy, even if subtle. Rates range from 13 to 20 % [9, 15]. Mechanical considerations must also be evaluated. Hendren reports one patient who had narrowing just above the distal anastomosis where her substernal conduit passed behind the xyphoid and over the liver causing extrinsic compression of the colon [5]. Distal strictures do not appear to be as amenable to dilation, with four of five requiring surgical revision in the series by Ahmad [10].

Late Gastrointestinal Bleeding

Reports of late gastrointestinal bleeding are likely related to the scrutiny of the individual author and are likely driven by significant symptoms warranting surgical attention. Bassiouny reports no occurrences, although no obvious surveillance program was utilized [6]. Lindahl found one anastomotic ulcer at routine follow-up when pallor was noted on physical examination and anemia confirmed by laboratory investigation [9]. Coopman reports anemia in 18 % of his cohort, and Ahmad notes one severe ulceration requiring graft replacement [10, 11].

Hendren details his experience with 7 patients out of 32 with late gastrointestinal bleeding [5]. Most had a vagotomy and pyloroplasty at their original operation. This included one duodenal ulcer at 12 years postoperatively and one gastric ulcer at 13 years. Both healed with appropriate medical therapy. One child developed gastritis 3 years postoperatively, with partial pyloric obstruction which was relieved by pyloroplasty. One patient developed bleeding from an anastomotic polyp 8 years postoperatively which was resected. One child developed a large paraesophageal hernia of the stomach into the chest 6 years postoperatively, which presented as bleeding which was repaired. Two patients had a small amount of gastrointestinal bleeding for which no source was discovered both ceasing spontaneously.

Interestingly, gastrointestinal bleeding has not been emphasized as an important complication in most series but is encountered in up to 25 % of cases followed long term. The etiology of bleeding has included paraesophageal hernia, gastric outlet obstruction with gastritis, peptic ulcer disease, and alkaline gastritis. If bleeding is encountered, the patient should be studied by upper gastrointestinal series, endoscopy with biopsy, and the measurement of gastric pH, to document possible alkaline gastritis which should be treated appropriately.

Intestinal Obstruction

The occurrence of bowel obstruction is on par with that expected from large series of patients undergoing laparotomy. Most authors mention bowel obstruction only when operation was required. The etiology is most commonly due to intestinal adhesions with rates ranging from 3 to 7 % [5, 8, 12, 15, 17, 18].

Hendren reports one obstructive episode due to small bowel intussusception [5]. Ahmad reports 4 patients of 38 who had an intrathoracic obstruction, of whom 3 required operative intervention [10]. The occurrence of volvulus in a retrosternal interposition has been reported in two [26, 27].

Pulmonary

Rigorous testing of pulmonary function is not commonly reported in most series. Coopman

notes that half of their population has either asthma, recurrent pneumonia, or recurrent bronchitis. However, these rates were equivalent to those reported in the overall esophageal atresia population and are not likely due to the colonic interposition itself [11]. Lung function testing was undertaken in 12 with only 5 (42 %) having normal function. Restrictive lung disease was noted in 50 % with a TL <20 %. Of these five had a spinal deformity and two had respiratory insufficiency with hypoxia and/or hypercapnia. Two of the 12 (16 %) had obstructive lung disease. Late pulmonary restrictive disease was noted in 20 % by West and was attributed to recurrent episodes of aspiration despite antireflux precautions. This was improved by the later addition of a gastric drainage procedure. The performance of pyloroplasty with the initial operation has greatly improved pulmonary sequelae.

Nutrition and Growth

Nutrition and growth data have been recorded in several series with variable findings. In general, patients with colon interpositions tend to be small and underweight. The underlying diagnosis leading to esophageal replacement has a clear impact. Kelly provided a 13-year follow-up in which those with caustic ingestion were in the 45–50th percentile and remained constant. Those with esophageal atresia were initially at 12 % and then increased to 33 % during the study, therefore demonstrating catch up growth [8].

Growth curves remained in the 5th–50th percentile over a 15-year follow-up in a series by West et al. [17]. Burgos noted 9 % (5 of 53) to be under the fifth percentile [7]. Rode noted 5 of 16 to be growth retarded, but 75 % had a normal growth velocity [16].

German/Waterston assessed long-term nutrition and growth in esophageal atresia patients who were greater than 10 years after operation, including those requiring esophageal replacement. Weight percentiles were 25 % in the EA group and 3 % in those with colon interpositions. However, diffuse overlap exists. In the 12 EA cases (eight of whom had other anomalies), seven had a preoperative weight below the tenth percentile. Six of these seven remained below the tenth percentile for weight. Four were below the tenth percentile for both height and weight. Three of them were above the tenth percentile for height. Five of the atresia cases were above the tenth percentile for weight preoperatively. Four of the five remained above the tenth percentile for both weight and height. Only one fell behind who had multiple anomalies. Six of the eight with another malformations remained below the tenth percentile. The four with three or more anomalies all remained below the tenth percentile for both height and weight on long-term follow-up.

In the eight non-atresia patients followed for more than 10 years, seven were at the same percentile or better than originally. Long-term growth correlated well with the preoperative status of the child. In atresia patients growth correlated with weight preoperatively and the presence or absence of associated anomalies. In the others, growth was excellent in all but one patient.

Coopman performed a dietary intake questionnaire in nine patients. Despite all meeting or exceeding the RDA (106 %), 25 % had undernutrition on growth metrics. No improvement in nutritional status was noted over time [11].

Therefore, this unique cohort may require increased energy intake from potential chronic respiratory disease or malabsorption due to colonic bacterial overgrowth, diarrhea, or vomiting. Lindhahl noted significant fat malabsorption in 2 of 15 [9].

Interrogation by sophisticated testing such as malabsorption screening and calorimetry may be considered in selected patients.

Delayed Puberty

The onset of puberty was delayed in 22 % in a series by Coopman with an average onset at age 11 in girls and age 13 in boys [11]. His is the only series that provides information on sexual development, which may possibly be a surrogate for nutritional status.

Spinal Deformities

The prevalence of spinal deformities is not routinely reported but appears to be quite prevalent with chronic backache, the most prevalent symptom. Scoliosis is reported in 22–34 % and kyphosis in 6 % [7, 11]. The etiology is diverse and attributed to associated congenital vertebral anomalies, postsurgical changes, and idiopathic. Radiographic screening is supported.

Endoscopic Surveillance

Endoscopic screening for the early detection of colorectal cancers is recommended in many large populations. Hsieh described a metachronous adenocarcinoma in a colon conduit following treatment of an intra-abdominal colon carcinoma. The use of a colonic conduit with potential exposure to an acidic or alkaline environment has been thought to theoretically increase this risk. However, his literature review of nine cases reported only one at the cologastric junction, not supporting exposure to gastric and/or bile juice as playing a major etiologic role [28].

Khan performed endoscopy in 13 of 25. Mild histologic colitis was common, but none had metaplasia, aneuploidy, or colonic dysplasia [12]. Rode had one of four patients with multiple shallow ulcers in the colon just above the gastric junction and a small solitary single diverticulum. Significant diverticular disease has not yet been reported in colonic transplants. As the colon interposition population is aging, consideration for routine screening protocols is encouraged [11].

Oral Diet and GI Symptoms

The ability to support one's nutrition on solely oral feeds is perhaps the metric or yardstick by which one measures the ultimate success of an esophageal interposition. Hendren reports that the ultimate ability to swallow and eat a normal diet is the rule after colonic substitution and is supported by other authors [5, 13].

Other authors report mixed results. Ahmad report that 91 % achieve oral feeds by discharge, with the remainder dependant on gastrostomy supplementation [10]. However, 45 % in his series required further surgery to achieve and maintain a good functional result.

Minor symptoms are quite prevalent and are likely the results of close scrutiny.

Dysphagia in the absence of an anatomic stricture is not uncommon. Most have mild dysphagia to certain foods and report a sensation of food "catching" which is relieved by water ingestion. These symptoms tend to improve with time. Endoscopy for food impaction is occasionally required. Coopman queried 20 patients, and all but one had persistent swallowing difficulties with feeding difficulties in half [11]. Kelly reported that 86 % had no dietary restrictions and were able to eat food at relatively rapid rates. However, 9 % ate small meals, 9 % had bloating after a large meal, and 9 % reported a subjective "sticking" of food in the throat despite normal contrast studies [8]. Lindhahl reported normal swallowing in 9 of 15 (60 %), with four having difficulty with meat and oranges, and one with occasional regurgitation in the supine position [9]. Hendren and others note bulging in the left neck in most patients during passage of the food bolus. Most become quickly accustomed to it and some massage their neck to promote swallowing [5, 12, 15].

Notable borborygmi occurs during and after meals in 62 % [16]. Other minor symptoms can include abdominal pain (60 %), dysphagia (50 %), and a prolonged time to ingest meals. Khan emphasizes the need for all patients to maintain an upright posture particularly when eating, drinking, and sleeping and suggest gravity is the most important mechanism for conduit emptying. A substantial number of patients have coughing while eating (40 %), diarrhea (40 %), substernal postprandial heartburn (35 %), halitosis (20 %), and regurgitation/vomiting (20 %). Nearly one quarter of patients remain on medical treatment.

Khan studied 19 patients with a barium swallow. All had rapid transit of the liquid bolus and emptying without any significant delay or holdup [12]. Fluoroscopy shows that the ingested bolus is transported more by gravity than by the rapid

peristaltic activity seen in a normal esophagus. Rode also studied the transit time from bolus ingestion to reaching the stomach. For fluids, this varied from a few seconds to 2 min in an unobstructed conduit. Transit time for solids ranged from 2 to 25 min on average, with one taking nearly 2 h to completely clear. Transit time for solids was greatly improved by taking fluids with the meal [16].

Manometry

Manometric evaluation of the colon conduit has been reported by Rode in three patients with excellent results. Basal colonic pressures were 14 cm of water, but no spontaneous peristaltic activity was observed [16].

Late Mortality

Late mortality is exceedingly rare and has not been related to GI pathology or complications of the conduit [5, 10].

Quality of Life

Assessment of the overall quality of life has been increasing reported. Overall subjective assessment of children by parents stated that 17 of 20 were doing "well" [11].

The completion of schooling and the quality of social life was essentially normal in a series reported by Ahmad [10], with almost all achieving age appropriate goals; none claimed social limitations. Burgos studied the Karnofsky Performance Status Index which was originally applied to cancer patients. This tool assesses functional performance, side effects of treatment, and disease-specific symptoms and utilizes a quality of life (QOL) questionnaire to query subjective perception of well-being and familial and professional adaptation. All patients were over age 18 with a median age 38 years. In a mean follow-up of 33 years, 60 % were healthy with a good/excellent functional outcome. Thirty-six percent had a fair outcome with mild lifestyle limitations, and 4 % had a poor outcome, typically due to persistent dysphagia and/or chronic respiratory disease. Overall, there was good functional outcome and a perception of good health. He noted that symptoms improve over time and that there was, importantly, no correlation of immediate postoperative complications to the long-term QOL [7].

Ure provides one of the most extensive QOL reviews [29]. He examined 58 esophageal atresia patients; 50 had a primary anastomosis and 8 underwent a retrosternal colon interposition. Three assessment instruments were used: a global QOL scale, the Spitzer Index, and the Gastrointestinal QOL Index. A lower QOL was noted in interposition pts, with the QOL in primary anastomosis patients equivalent to healthy controls. Similar scores were demonstrated between healthy controls, those having a primary anastomosis, and colon interposition patients in physical and social functions and emotional state. Interposition patients suffered more overall from various gastrointestinal complaints (eating habits, meal capacity, and the requirement of liquids with meals). Five of eight had a sensation of holdup; some had pain and choking with swallowing, nocturnal regurgitation, and respiratory symptoms. All interposition patients subjectively felt short of breath. A restricted meal capacity was seen in 62.5 % versus those with a primary anastomosis, but they led an otherwise normal life. Overall, lower scores were attributed to GI symptoms. The long-term QOL was acceptable, suggesting those with congenital malformations may acquire coping habits.

Lastly, Khan measured functional outcome according to a classification scheme proposed by Ahmed and Sptiz. Overall 52 % had excellent results (asymptomatic, tolerating a regular diet), 28 % had good results (asymptomatic with minor dysphagia), and 20 % had fair results (significant dysphagia) [12]. Long-term follow-up of these challenging pediatric patients is essential far into adult years.

Conclusion

Colon interposition surgery is technically challenging and is reserved for the rare case in which the native esophagus cannot be

preserved. Colon interposition is a safe operation with rare mortality and low morbidity which requires meticulous surgical technique and diligent follow-up. Complication rates may reach greater than 80 % and are related to the length of follow-up. Perseverance in the management of complications is necessary as many present in the decades following the initial operation. Surgical revisions are often required. Follow-up, which extends to 25 years in some series, have shown very satisfactory long-term results [5]. In Hendren's experience, the colon conduit provides an excellent substitute esophagus for pediatric patients. The operation should have relatively low rate of major complications, most of which are avoidable and most of which can be corrected to give quite good to excellent long-term results in the majority [5, 8, 10, 11].

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57 The Long-Term Follow-Up from the Parents' and Patient's Perspective

J. Trompelt

Situation in Germany

The German healthcare system offers good surgical and postoperative care to children born with esophageal atresia (EA). If the diagnosis is made early, mortality from isolated EA, with or without tracheoesophageal fistula (TEF), is nowadays very low. Death of a child suffering from EA is mostly due to severe associated malformations, primarily cardiac defects, or chromosomal anomalies that are incompatible with life or prematurity [1–4].

EA, as a rule, does not represent a lethal malformation today. This heightens the significance of other qualitative aspects: incidence and management of potential complications, morbidity and quality of life of patients during their childhood, adolescence, and adult life.

Local medical care, as pursued in Germany, is positive for the parent-child relationship, but in rare malformations may also prove to be disadvantageous. In Germany, about 220 EA patients are born per year (incidence, approx. 1:3000, about 670,000 births annually). These will be admitted to a total of almost 100 pediatric surgical wards and departments as well as a few clinics for adult care. There are only a small number of wards and hospitals caring for more than one to three newborns with EA per year. This means that only few physicians have the opportunity of deepening their academic knowledge by personal experience. Personal experience, on the other hand, influences the surgical outcome, the quality of follow-up care, and the assessment of complications or sequelae [5–7]. Limited routine or lack of experience on the part of the medical staff may mean that complications and sequelae are not followed thoroughly or at all. Further, the treatment implementation could be delayed or the scope of treatment is suboptimal. This, in turn, may lead to increased risks, especially of gastrointestinal or respiratory complications, which may affect a patient's physical and psychosocial development. This experience is shared by the Patient Support Organizations (PSOs).

PSOs are not merely an important source of information for families and patients. Families also experience the relief of knowing that they are not alone and they are able to profit from the knowledge of other people, who are in the same situation.

Over time, PSOs gather profound experience on pertinent subjects, like malformation, sequelae and associated disease, treatment options, and the individual effects, which EA will have on the everyday lives of patients and their families. On this basis, PSOs offer counseling, orientation, and assistance in coping with the disease and its consequences. The German PSO (KEKS e.V.) was established in 1984. The experience gathered

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by this organization is also available to the medical profession.

Prevalence of Frequent Complications as Well as Secondary and Associated Diseases, According to the KEKS Database

Many physicians presume that it is only the severely affected patients or those suffering from medical malpractice who gather in PSOs. They suspect that the experience accumulated in our organizations may tend to have a negative tinge.

For that reason, the KEKS e.V. PSO carried out a member survey and evaluation of their member database (out of 780 member families, 236 questionnaires were returned in 2004). The prevalence of EA types, complications, sequelae, and secondary surgical interventions as recorded by the PSO was analyzed against data in the literature [8–16]. The percentage of long-gap atresia in the PSO was twice as high as that given in the literature (Fig. 57.1). While some complications or secondary interventions in the PSO slightly outnumbered those in the literature, others were underrepresented by comparison or largely corresponded to the data in the literature (Fig. 57.2).

A high percentage of PSO children suffering from tracheomalacia were subjected to aortoventropexy (35 % of those affected). It is possible that cases of low-grade tracheomalacia were not included in the diagnosis or, given the EA, were considered normal. The prevalence of typical associated malformations was rather lower than was expected (Fig. 57.3). It is likely that families primarily seek the help of a PSO for malformations that appear to them as being the most menacing – medically or personally – for instance, they might consult an organization for children with cardiac disease in the case of severe concomitant heart abnormality.

Long-gap atresia is essentially overrepresented in the member database. This fact, notwithstanding, the excess of serious complications and sequelae in the member population is quite low, meaning that complication rates among PSO members were not greatly increased.

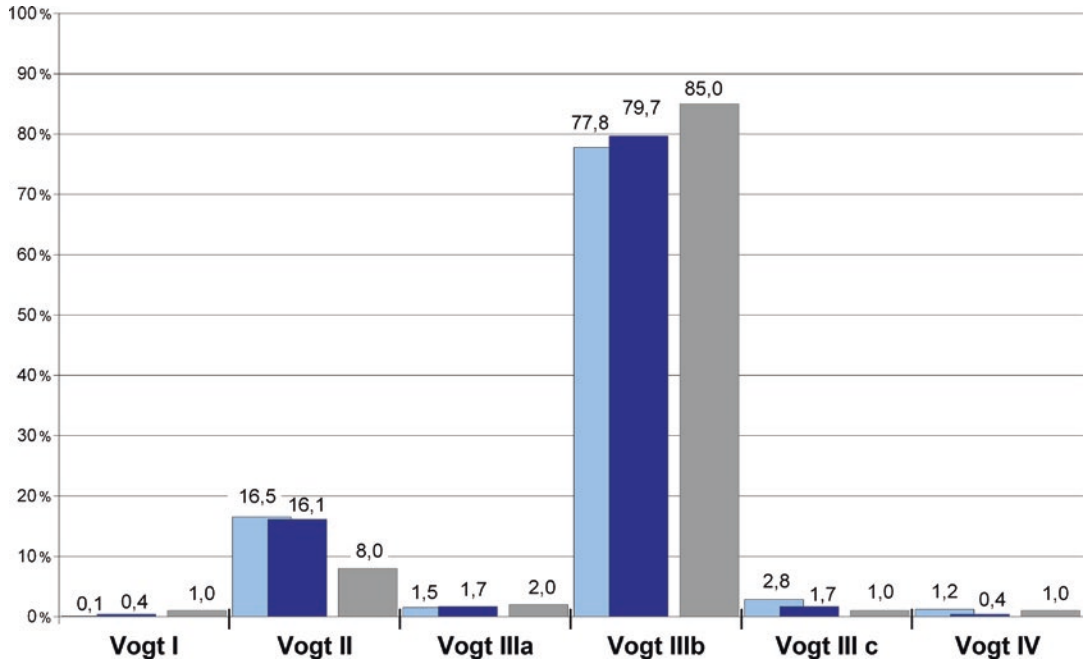

Fig. 57.1 Prevalence of EA types in the German Patient Support Organization (KEKS e.V.) (According to Trompelt et al. [17]). Database KEKS e.V. Survey KEKS ($n = 236$). Literature [4]

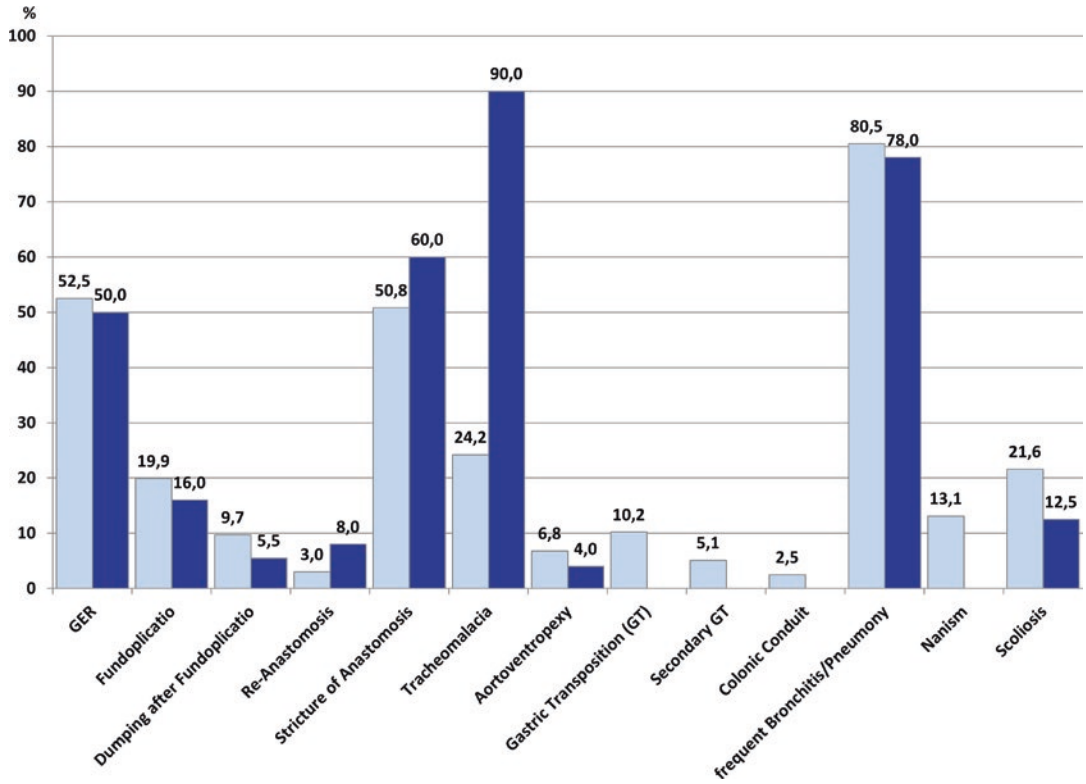

Fig. 57.2 Prevalence of complications and further surgery in the German Patient Support Organization (KEKS e.V.) (According to Trompelt et al. [17]). Survey KEKS e.V. ($n=236$). Literature (approximate value [4, 9, 12–14, 41])

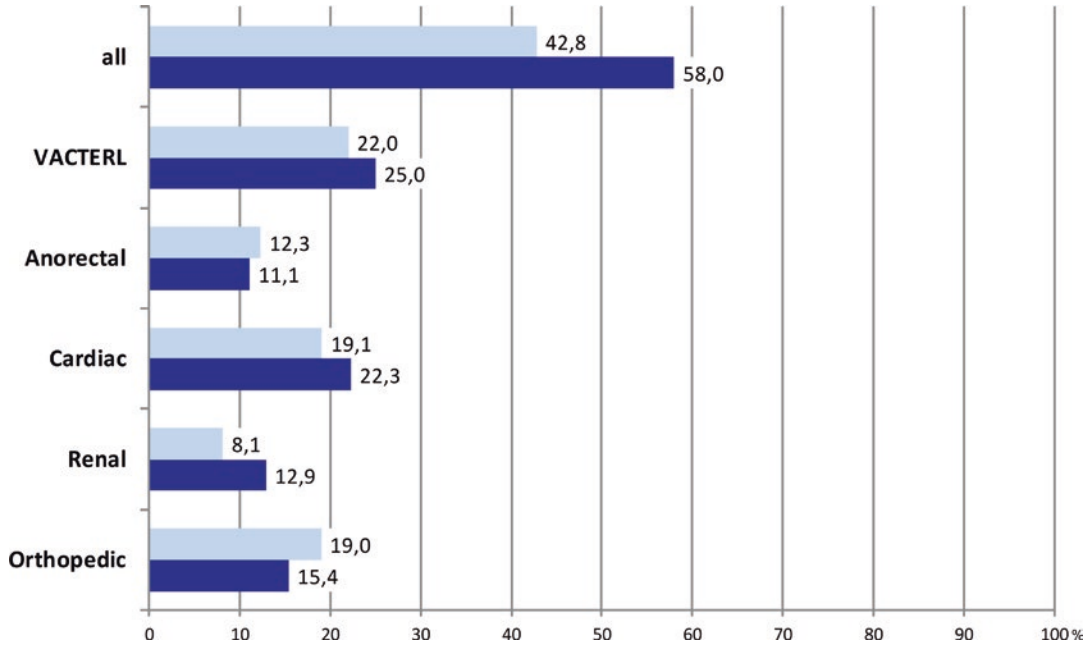

Fig. 57.3 Prevalence of associated malformations in the German Patient Support Organization (KEKS e.V.) (According to Trompelt et al. [17]). Survey KEKS e.V. ($n=236$). Literature (approximate value [4, 10, 11])

Impact of Complications and Secondary Diseases on the Everyday Life of Patients and Their Families

Family Education

The personal experience of the surgeon or the physician providing aftercare will influence the state of information of the family and thus their ability to cope with potential problems [18–20]. PSO observations indicate that a patient's or family's handling of an existing malformation depends on their state of information and education on the subject. Their tolerance of complications hinges upon prevailing expectations: Families, for instance, to whom even grave difficulties in swallowing were described as being normal, may accept considerable constraints for a (too) long time without seeking help.

Case Report

By way of an internship, a 17-year-old, considerably underweight girl with EA came into closer contact with the PSO. It was noticed that she was able to only take in small amounts of food, she needed to be washed down with drinks, and she preferred soft mushy food. When asked about it, she said that she had always had difficulty swallowing and that this was normal since she had esophageal atresia. She agreed to undergo endoscopy upon the recommendation of the staff. Findings showed severe stenosing of the anastomosis. After repeated bouginage, the young woman is now able to enjoy completely normal food and experiences substantial weight gain.

If, on the other hand, expectations are raised that a child will be completely well after the surgery, complications are often seen as parent or surgeon failure, and their existence may be denied for as long as possible by one party or the other. This makes it difficult to keep up a trustful relationship between doctors and parents.

Parents' Report

We were told that our child would be completely well after the surgery and that in case of any problems, they would be experienced enough to deal with them. However, they could not offer any solutions when our child had repeated episodes of apneic spells. Instead, we were told that it was not known what caused them and that this was not an issue of pediatric surgery, anyway. It was only in another hospital that our daughter was diagnosed with severe tracheomalacia.

In no case information of the family must be limited to the preoperative or immediate postoperative discussion. Parents and patients are personally affected and fearful, so that they often will not be able to immediately realize the significance and implications of findings and diagnoses for their lives. It is indispensable to continue having sympathetic and caring conversations with a child's parents. The potential or existing complications and problems typical of the child's age need to be discussed without discouraging his parents.

When problems arise at home, many families seek additional information beyond what they receive from the doctors. Today, the Internet is the information source of choice but unfortunately not all websites are trustworthy. Therefore, PSOs have improved their communication efforts. By and by an increasing number of patients are being guided to appropriate PSOs. In turn, they can contribute to patient information and education based on their respective, extensive experience.

Parents and patients need to know that after successful surgery the esophagus will not be completely normal, even if no postoperative complications occurred. They need to be informed that there is a risk of complications and sequelae, which may be treated or must be treated, depending on the situation. It is only informed families who are able to be relevant and competent partners

in the timely diagnosis of potential esophageal and respiratory functional impairment secondary to EA.

In Hospital and Back Home

Shortly after birth and during the immediate postoperative time, the family's concern about the life and future of their child is in the foreground. The initial joy of having a child rapidly gives way to great anxiety: "Will my child survive the surgery? Will any damage remain? Will my child ever have a normal life?" Most parents cling to the hope that the surgical intervention will solve all problems and that their child will be restored to perfect health. Medical statements to this effect are gratefully absorbed. Should complications occur, the parents' confidence in the doctor will be severely shaken.

Accepting that a child has a health problem that will stay with it all its life is a difficult process. Any complications or new findings (e.g., additional malformations) will inevitably throw parents back to the beginning of their adaptation process. It is only by repeated sympathetic and honest discussions of the individual perspectives of a child that a trusting patient-doctor relationship can be build and that families are able to confront themselves in a timely (though painful) manner with the significance of the malformation for their lives.

As a first step, the child needs to undergo surgery so that the continuity of the alimentary canal is restored. The child may have to go through potential complications, such as anastomotic leakage, infections, pneumothorax, and recurrent tracheoesophageal fistula that may develop immediately after the surgery. The subsequent target is the complete oral feeding of the child and its discharge from the hospital unless this conflicts with additional malformations or health problems.

Parents often feel insecure when their child is discharged from the intensive care unit with all its continuous monitoring to the regular ward. Depending on the child's history, release from hospital may also create a considerable amount of ambivalent feelings for the family: On the one hand, there is that natural desire to take responsibility for one's own child and its feeding and recovery which up to that point were mostly provided by doctors and nurses. On the other hand, parents are afraid that they may not be competent to meet the special needs of their child. The situation is aggravated by the parents' sadness over a child with compromised health:

Family Report

"Home at last!" was our first thought. Our son had overcome many complications and I was even able to nurse him. But we were unable to find our peace of mind for fear that we'd have to get him back to the hospital if he would not feed properly. We had been told to weigh him before and after breast-feeding. But how do you weigh a hungry crying baby with some precision? So I felt tense all the time which did not contribute, of course, to proper nursing.

PSOs and sociopediatric aftercare institutions (e.g., in Germany "Bunter Kreis") offer support to families in this situation.

The problems each family will face at home vary with their children's preconditions.

Feeding Problems

Feeding and nursing represent the elementary forms of maternal attention to a child and therefore are a core topic for the family concerned.

EA conflicts with the natural desire of a mother to feed her child. Complications following anastomosis surgery or replacement of the esophagus may contribute to difficulties in oral feeding as well. Mothers often consider that drinking and feeding problems, frustrating tube weaning, or unsatisfactory weight gain are their personal failure. This may put a massive strain on the mother-/parent-child relationship. An understanding approach, therefore, is necessary when dealing with the families of EA children who do

not drink or feed adequately. Psychological support of a family may be helpful, especially during the period of tube weaning and establishment of full oral feeding. It is important to not only focus on weight gain but also to consider the complete picture of a child's development. Families feel considerable relief when – during tube weaning – the child's general condition and advances in development are included in the assessment of its medical status.

Feeding and food texture should be as normal as possible for a child's age. A child, who under medical aspects is able to eat and drink, will do so or learn to do so very soon. A physical cause will probably be at the root of failure to thrive or eating disorders, if a child refuses oral food intake as a matter of principal, avoids age-appropriate food, or fails to thrive properly. This holds particularly true in children with EA. Psychosocial causes of refusal are more likely in children growing up under highly unfavorable socioeconomic circumstances [21–23].

The German PSO carried out a study into the development of eating attitudes among their members [24]. It showed that the time to reaching so-called milestones (complete oral feeding, liquid food, mushy food, and adult diet) depended on the severity of the EA and accompanying malformations, complications, and sequelae (Fig. 57.4). The same is true for the enjoyment of food and the pace of food intake (Figs. 57.5 and 57.6). Depending on the history and complications, complete oral and age-appropriate feeding of an EA child may be delayed, but remains the defined and almost always attainable goal of treatment.

Infant Drinking Problems

Causes for drinking problems after early correction are to be found among the complications that are typical of a given EA pathology, such as massive anastomotic stricture, TEF or recurrent TEF, gastroesophageal reflux (GER), or tracheomalacia. These causes need to be tracked down, even where other factors, like prematurity, accompanying malformations, or disorders, are present at the same time. The exact history of drinking behavior is essential for tentative and differential diagnosis, and specific attention to gagging, drooling, coughing, increased stridor, or dyspnea including apnea is required.

Tube Weaning

After short-term tube feeding in early uncomplicated esophageal anastomosis, tube weaning will pose no problems in most cases. Difficult drinking and tube weaning problems mostly concern children, in whom oral food intake was not possible for a prolonged period of time (e.g., long-gap atresia, prematurity, complications, or additional malformations precluding any attempts to establish oral feeding). In these cases the time span to achieving age-appropriate nutrition is distinctly longer than in uncomplicated cases or healthy children (Fig. 57.4).

Results of our PSO survey, which were confirmed by many families, showed that sham feeding had a sustained positive effect on eating attitude. This approach combines tube feeding with the oral feeding of fluid draining via a collecting tube or esophagostoma (Fig. 57.5). Since sham feeding without an esophagostoma may be problematic, careful weighing of the expected benefits against the potential risks (aspiration!) is indicated. As a minimum requirement, oral stimulation – e.g., by a pacifier dipped in sugar solution or tea – should be possible.

Without sham feeding or oral stimulation, the baby can neither train his sucking reflexes nor his oral motor skills. Disagreeable oral experience like manipulations such as intermittent suction or elongations without analgesic sedation or anesthesia will make the change to oral feeding even more difficult.

For tube weaning to be successful, the child must have an incentive to eat and drink. In children, who were exposed to negative oral experience, fears and unpleasant associations may often outweigh the pleasure gained from tasty food or repletion. Hunger and thirst are the strongest physiological stimulation to take in food and drink. Trivial as this statement may be, it is often not considered by parents or doctors for fear of a weight loss.

In the experience of the German PSO, parents and doctors misunderstand that weaning attempts fail, if at the same time, the energy demands of a

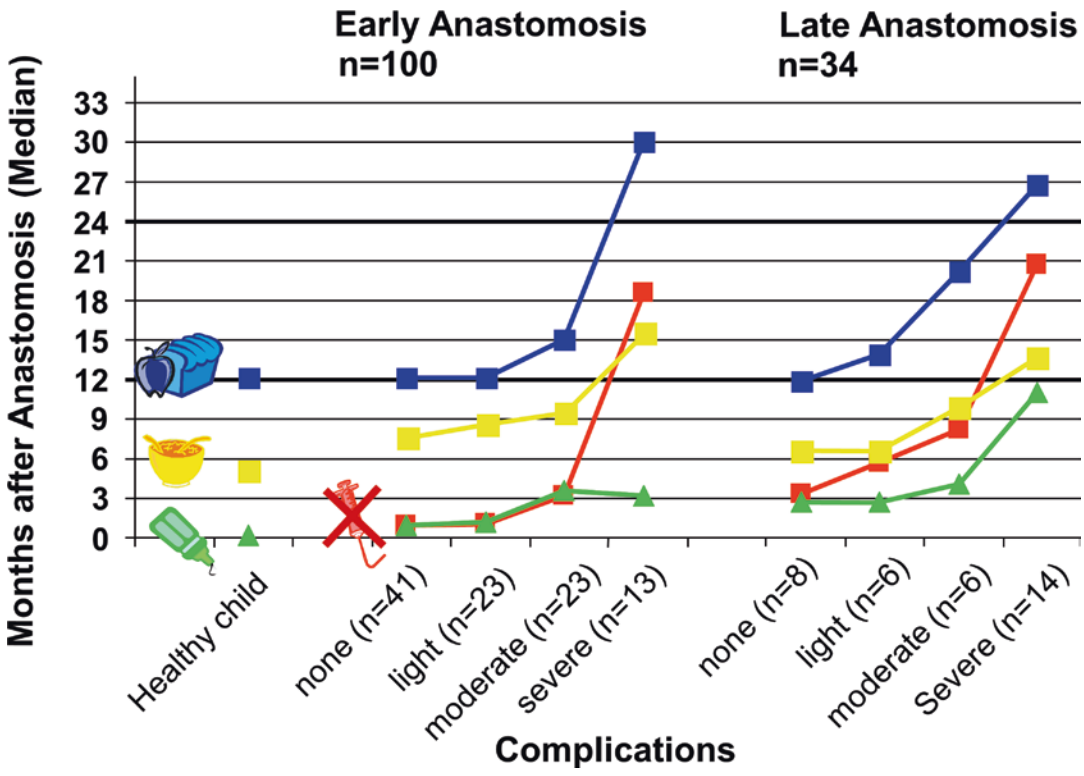

Fig. 57.4 Milestones of oral food intake (According to Trompelt et al. [24]). Stop of tube feeding. Liquid food. Mushy food. Solid food

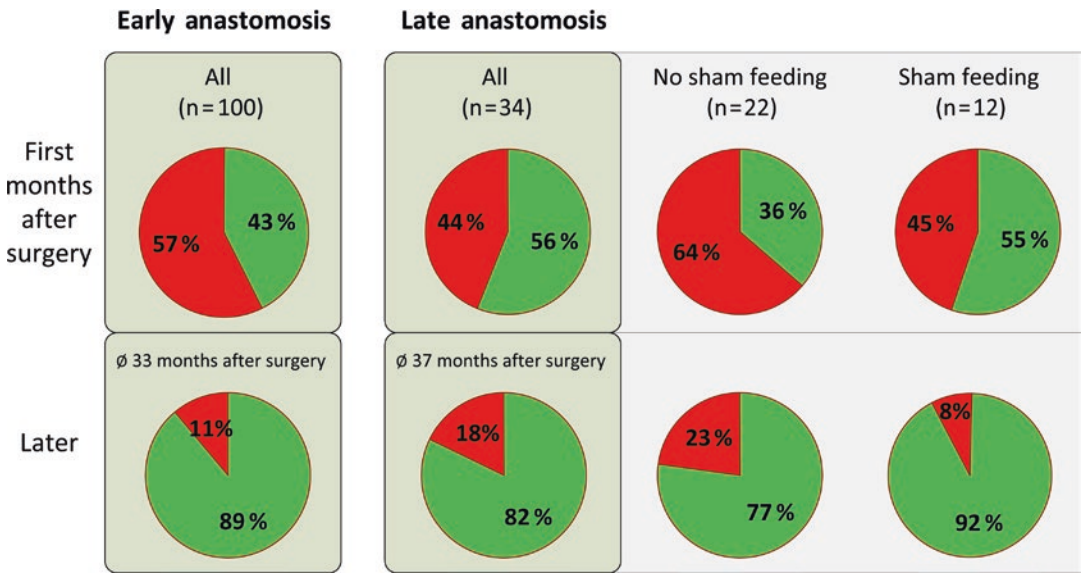

Fig. 57.5 Attitude to oral nutrition of EA children after anastomosis (According to Trompelt et al. [24]). Unwillingly/only forced. With pleasure/willingly

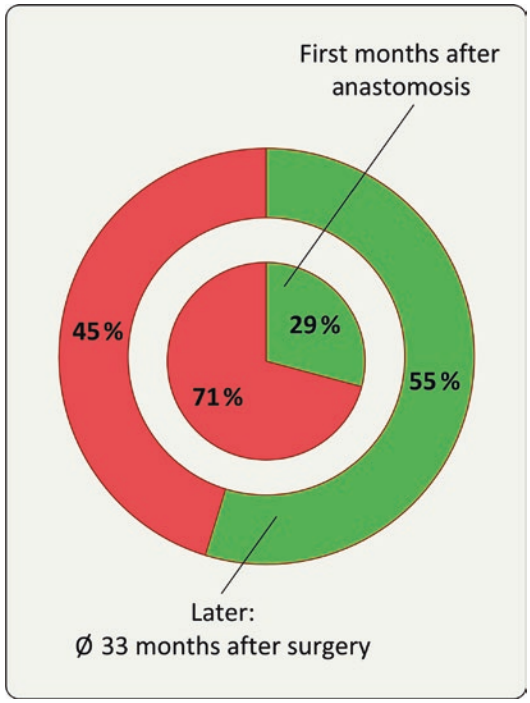

Fig. 57.6 Duration of meals (According to Trompelt et al. [24]). Child needs substantially more time than its peers. Child needs about the same time like its peers

child are fully met by feeding via a tube or gastrostomy. It is often presumed that a child eats sufficiently before tube feeding is being reduced or discontinued. But weaning can only be expected to succeed if the child is allowed to feel hungry.

To promote its oral motor skills and normal social development, it is necessary that the child should feed orally as soon as possible. Especially in small infants, the nasogastric tube itself can possibly impair swallowing. Once the medical obstacles have been cleared, the pediatric surgeon and the pediatrician should work together to provide an individually tailored concept for tube weaning to be implemented as soon as reasonably possible.

In its initial phase, tube weaning will be associated with weight loss. An infant with long-term tube feeding has not been able to experience the causal connection between oral food intake and repletion. Hence many children do not feed at all or food uptake is clearly not enough during the first stage of tube weaning. In the experience of the PSO, weight loss is all the higher if preceded by attempts to overnourish the child. Pediatric care is required for the medical monitoring of the child during tube weaning. Psychological guidance may help parents in stages of feeding refusal.

If the problems with tube weaning persist, the concept needs to be revised, so that new medical obstacles may be identified and handled, if possible. If tube weaning at home fails, inpatient weaning with an experienced team may be considered.

Problems Arising When Feeding Is Switched

As for any child, normal age-appropriate nutrition is also aimed at for children who underwent EA surgery. Problems arise especially when a child is switched to semisolid or solid food: Food refusal, which is more pronounced than in normal children during an adjustment process, gagging, vomiting, or respiratory distress has a medical background in most cases [9, 25–28].

Experience shows that in infants, anastomotic strictures may often go unnoticed since milk is a thin fluid and will pass even narrow strictures. Only thickened milk or switching the feeds to semisolid or solid food will lead to clinically manifested swallowing problems or can result in food-bolus impaction, which might be resolved endoscopically, if necessary.

Even in older children or adults, anastomotic strictures can go undetected for a long time. Sometimes patients prefer rather fluid food and their environment does not realize that there might be a problem behind it. Therefore, a regular and specific inquiry into eating habits and food consistence is needed.

Early radiological and endoscopic follow-up evaluations of the esophagus are recommended to avoid negative swallowing experience. Experience shows that bougienage is achieved more easily if the scarring is relatively new. Follow-up examinations, therefore, are helpful even in the absence of clinical signs and prior to feeding being switched, i.e., at the age of 4–6 months at the latest.

Depending on their level of information and their personal experience, some families tend to be overcautious. A timely follow-up may help to reduce fears associated with the switch in feeding.

Swallowing disturbances may often deteriorate only very gradually and go unnoticed since the

children and their families are adapted to impairments of swallowing, due to motility disorders that are present in most cases. This experience is shared by the PSO as well as by the author and her son. Irrespective of complaints of deterioration by the patient himself/herself, regular follow-up checks are recommended and need to include meticulous anamnestic recordings of swallowing as well as observation of a child's eating behavior.

Failure to Thrive

When an EA child fails to thrive, there are typical causes that must be considered, more or less pronounced swallowing disturbances, frequent bronchopulmonary infections due to gastroesophageal reflux, tracheomalacia, or a recurrent TEF, but also increased breathing effort in severe tracheomalacia should be evaluated.

Dumping syndrome is also to be taken into account in EA patients with antireflux surgery (fundoplication) [12, 25, 27] and patients with gastric transposition [29]. Recent reports show that – as a rare incident – this syndrome may occur in postoperative EA even without fundoplication [28]. PSO experience shows that the signs and symptoms may not be understood for a prolonged period of time. Sometimes such misinterpreted symptoms are revealed only after more examinations became necessary due to the random finding of postprandial glucosuria or if malabsorption-induced iron deficiency anemia, osteoporosis, or hypovitaminosis occurred.

Many parents have experienced that increasing caloric density has little effect on the thriving of EA children. They just eat less to compensate. It is important to search for the underlying causes and subsequently provide adequate treatment.

Gastroesophageal Reflux (GER) and Gastroesophageal Reflux Disease (GERD)

GER is a typical and very frequent complication of postoperative EA [30, 31]. Thickening the food may offer some relief of the GER cardinal symptom "chronic recurrent vomiting" which frequently affects infants. It is often absent in older children where nocturnal coughing and recurrent respiratory disease are in the foreground in most cases. GER, in particular in infants, also may be associated with life-threatening episodes due to reflex apnea and massive aspirations. Typical differential diagnoses in EA patients (esp. with TEF) include tracheomalacia and an additional or recurrent TEF.

In children and adults who underwent EA surgery, the cardinal symptom "heartburn" often is absent because innervation of the distal esophageal segment is diminished.

GER may be the reason of recurrent anastomotic strictures and ineffective bougienage. Therefore it must be ruled out or treated in these cases. Furthermore, GER may increase the risk of Barrett's esophagus and esophageal adenocarcinoma [2, 26, 32–34].

Additionally, GERD-induced chronic esophageal hemorrhage can induce anemia.

In most cases, GERD becomes evident in the first years after esophageal repair, but may also develop in later years. It is conceivable that a surgically treated esophagus is particularly prone to develop GER-induced mucosal lesions due to its reduced clearance [33]. Regular monitoring of the esophagus including endoscopy with biopsies is therefore recommended as a long-term measure to be followed into adulthood.

Surgical management of GERD in EA patients must consider the restricted motility of the distal esophagus segment [34, 35]. A tight fundoplication, especially Nissen's fundoplication, may make oral nutrition very difficult, since due to its compromised motility, the esophagus segment that is distal to the anastomosis is hardly able to assist in the passage of food. This increases the risk of dysphagia, which may result in failure to thrive or problems in tube weaning as experienced by the PSO.

Respiratory Problems

Impaired swallowing due to anastomotic strictures and compromised motility may entail aspirations. Aspirations also may be caused by undiagnosed or recurrent TEF and by GER (see also section "Gastroesophageal Reflux (GER) and Gastroesophageal Reflux Disease (GERD)").

These conditions may precipitate pneumonia or pulmonary damage as well as cyanotic and apneic attacks, and a careful search for such causes is mandatory in frequent, severe bronchopulmonary infections requiring antibiotic treatment.

In infants and small children, frequent infections, especially of the respiratory tract, are normal physiological occurrences. Most children with congenital EA are suffering form tracheomalacia of a varying degree, especially if they had a TEF [13]. In this case, severe respiratory infections are more likely. The dominating symptom of tracheomalacia is a more or less audible stridor (usually more evident during meals). As a rule, low-grade or moderate tracheomalacia will hardly affect the child. Unless vascular malformation is the cause of tracheomalacia, the stridor resolves as the tracheal lumen of the growing child widens and the tracheal cartilages consolidate. However, the more pronounced the tracheomalacia is, the more tracheal clearance will be reduced compared to that of a healthy child, and expectoration of bronchial mucus must be accomplished against increased resistance. This produces bubbling breathing noises that typically persist till late infancy and intensify in infections and during meals. These children are prone to have severe pathologies when they contract respiratory infections, which may include pneumonias or require antibiotic treatment. Again, the intensity and duration of this susceptibility are determined by the severity of the tracheomalacia [36, 37].

Experience shows that mucolytic therapies do not considerably facilitate expectoration in EA children. They often lead to overproduction of mucus which will make breathing rather more difficult. From parental experience it is more helpful if the children receive a consistent respiratory physiotherapy similar to that received by children with cystic fibrosis guided by a well-versed physiotherapist. This should be completed by a consistent inhalation therapy, e.g., with saline solution.

The increased proneness to infections and the potentially higher breathing effort in tracheomalacia may lead to an increase in nutrient requirements. If there are simultaneous swallowing problems, proper thriving of a child may be at risk.

EA children with tracheomalacia have an extremely noisy and barky cough in particular in infections or allergic reactions. They, therefore, tend to attract negative attention, and explanations need to be given frequently informing people that coughing is a largely normal occurrence for the child considering the circumstances.

In general, tracheomalacia does not trigger life-threatening events. In a small number of cases, it may, however, be so severe that cyanosis or even obstructive respiratory arrest may occur [38, 39]. These attacks may be initiated by food passing the esophagus – especially if passage is affected (dorsal pressure on the trachea), in elevated blood pressure due to, e.g., crying (ventral pressure on the trachea) or infections (lumen is further reduced by mucosal swelling). Typically, children with severe tracheomalacia recline their heads in an attempt to widen the trachea. If stridor is present in combination with acute cyanotic or apneic episodes (also) during meals with or without head reclination, tracheoscopy under spontaneous breathing should be performed to exclude or confirm severe tracheomalacia. Once severe tracheomalacia has been confirmed, surgical intervention (aortopexy) should be considered even after the first occurrence of life-threatening conditions [38–41].

Experiencing life-threatening conditions like cyanosis or even apnea in their own child triggers extreme anxiety in parents. They will then adopt a particularly anxious and protective attitude toward their children in such situations:

Family Report

My son used to turn blue in the face over and over again, and even had episodes of respiratory arrest at home. Each time I ended up thinking: “That’s it, now he is dead.” When it was over, we would observe him anxiously for signs of any changes. We were extremely apprehensive that his respiratory arrests might leave him with cerebral damage. Our hearts would jump into our throats, whenever he turned blue. He had a

very noisy stridor that could be heard all day long and even in his sleep. He would always lie in bed with his little head far reclined. Whenever his breathing noise stopped, we knew he was in respiratory distress again. During nighttime we did not feel so bad since he was on the pulse oximeter. But during daytime, I felt that I had to keep an eye or rather "an ear" on him, always. I never dared to use the vacuum cleaner when I was alone with him because I would not have been able to hear him breathe. Aortopexy worked miracles: he was able to sit upright in his buggy and sleep with his head on his chest. He never turned blue again, not even when food got stuck in his throat.

Unless surgery is performed, a child in this condition is at risk to incur brain damage, if prolonged apnea occurs. Even if a child survives such episodes of oxygen deficiency, it is likely to suffer severe respiratory infections over many years (if not throughout life) due to its compromised bronchial clearance and is at risk for secondary lung damage.

In severe tracheomalacia GER following surgical EA repair represents an extra-challenge. The dorsal pressure on the trachea that is produced by vomiting or the reflux of food into the esophagus may trigger obstructive cyanosis or apnea. Moreover, surgical management of the reflux by fundoplication may impair esophageal passage to the extent that obstructive cyanosis or apnea is triggered or exacerbated. Documented evidence of three cases is available with the German PSO. In cases of severe tracheomalacia with obstructive cyanosis and apnea in comorbidity with significant GER or GERD, the indication for aortopexy should, therefore, be considered *prior* to an inevitable fundoplication.

As a result of rib synostosis, e.g., after thoracotomy, restrictive ventilation problems may impair physical fitness all throughout a patient's life [36, 42–44].

Esophageal Motility Problems

In EA children, the correction of the malformation entails esophageal motility impairment of varying degree. Most children quickly learn to accelerate the food passage through the esophagus mainly by "washing down." Bolus events due to impaired esophageal function are particularly likely if concomitant stenosis of the esophagus (predominantly in the area of the anastomosis) is present. While in most cases these "food catches" are associated with respiratory distress of a mild form, the severity of tracheomalacia determines the degree of respiratory distress. If there is high-grade tracheomalacia, food-bolus impaction may trigger life-threatening episodes.

The fear of bolus impaction may cause children and their families to be excessively apprehensive when eating, but also in everyday life. Some families shy away from offering their child solid food for a long time. They exercise extreme caution far beyond infancy and at least through the phase where small children put everything into their mouths. This attitude, however, may lead to social problems and to avoiding social contacts.

Orthopedic Problems

Associated skeletal malformations (primarily affecting vertebral bodies, ribs, or limbs) may call for conservative or surgical treatment.

Orthopedic problems may also occur as a consequence of one or more thoracotomies for EA correction. However, in patients without additional congenital deformities of the skeleton, scapula winging, chest wall deformities, or scoliosis, for instance, rarely reach a degree where they present more than a cosmetic problem [42]. This corresponds to PSO experience.

Social Problems

Young Children and Their Families

The problems occurring in the wake of EA may constitute a considerable burden for the family and the child.

Swallowing problems may cause failure to thrive. Eating a meal under these circumstances takes much more time and is exhausting for the child. The remaining time and energy to enjoy positive activities of the family and child and for playing are diminished. Preparing food and meals takes much more time than with a normal child.

Most children do not look sick, so that failure to thrive is often met with a lack of understanding in the child's environment. Advices like "have you tried porridge, mashed almonds, or this or that … yet," "don't distract your child's attention while his or her is eating" or "distract his or her attention," "you ought to make sure your child is getting more food," etc. may be to the despair of mothers involved. The only solution lies in a systematic search for causal factors; treatment of any medical causes, where possible; and honest and prospective information. The understanding that families receive from other affected people, e.g., in a PSO, is very helpful.

In certain situations, it is not advisable to intensify the therapy or there is no therapy available yet. In some cases, improvements will only be visible after healing or further growth of the patient. The empathy and support of other affected families and PSOs are of special value in these circumstances.

While eating primarily serves the uptake of nutrients, it also should be a pleasurable process. The worries whether the child's intake of food is sufficient, a mother's concern that her child might actually starve to death, may create a tense situation around every meal. This keeps a child from enjoying his drink and food.

Eating is also a social activity. Eating together makes food tastier; meals serve social exchange. If a child is not able to eat or suffers from vomiting portions of its meal repeatedly, this will constitute a burden for its social life and that of its parents. Family or friends may not always be sympathetic of lingering over meals or of the absorption of an EA child's family with meals. Some of these families finally tend to withdraw from all situations in which they and their child would have to eat in public.

Apart from the concern for their child's health, its @@proneness to contract infections adds to social isolation and means increased nursing care including physiotherapy and breathing therapy. Many children have noisy breathing even though they are not suffering from an infection. On an on-and-off basis, parents will have to defend themselves and explain that their child has no contagious disease and therefore does not need to stay home.

Especially during the flu season, many families seal themselves off and avoid or limit their contacts with other people and children in particular. Normal activities of mothers with small children, such as attending toddler groups or meeting other mothers with children of the same age, are drastically curbed or canceled altogether. Some parents hesitate to take their child to a day nursery or kindergarten, in order to avoid infection.

The increased attention and care given to the child with EA are a considerable burden for his or her siblings. In addition, not every marriage will stand the stress of a massive change in the couple's relationship that comes with the care for a chronically ill child.

Food-bolus events give rise to strong fears not only in parents but also in external caregivers. The families of the child's friends hesitate to invite the EA child over, because they are afraid of potential bolus complications.

Babysitting by friends and the close or extended family often is feasible only on a reduced scale during the child's first months or years. "You better take the kid with you, his breathing is funny," *or* "I'd rather not be responsible, if…"; those are sentences parents hear very often in this situation.

Depending on their personality, nursery teachers and school teachers may show concern or be afraid to admit a child. This means that families have to put in a lot of effort into convincing and reassuring people in charge, so that the child may attend a day nursery, kindergarten, or regular school. This may restrict the parents' options of working or finding help in dealing with their daily challenges.

Older Children and Adolescents

As with all chronic diseases, the restrictions associated with EA may have negative repercussions on the children's free time, on their social contacts, and also on their school performance.

In EA, it is predominantly the length of time needed for meals and the reduction in physical

performance due to respiratory diseases or lung involvement that may negatively affect free time, leisure activities, and social life.

Depending on a child's social environment, abnormal eating, barky cough, or restricted physical fitness may provoke offensive peer reactions or lead to social exclusion of the affected person. Experience obtained in the PSO shows that an open and confident attitude toward the malformation and the resulting limitations will increase the social acceptance of deficits or abnormalities:

Patients Report

In my new class, it was one student, in particular, who would always bark, if I coughed loudly. I attended a full-time school, and nobody wanted to sit with me for lunch, because I was eating so slowly and sometimes couldn't help gagging. I felt very unhappy. At one point, my parents proposed that I should present a paper during my biology class about esophageal atresia and the problems involved. That's what I did. My fellow students were impressed that I talked about it so freely. After that, the badgering grew less and by and by I even made friends.

Recurrent bronchopulmonary infections or frequent hospitalization may account for long times of absence from school which may have a negative influence on a student's performance and in turn may affect his further education and career opportunities.

Aftercare of Patients with Repaired Esophageal Atresia

Problems Arising from the Lack of a Consistent and Standardized Aftercare

While most late complications are evident only in the first years of life, they may also become manifest during growth spurts and even at adult age [2, 8, 12, 44–48].

If no aftercare is available, families are left alone with the problems that may occur. Whether and when medical help is sought for swallowing problems, failure to thrive or the signs and symptoms of GER will then largely depend on personal tolerance, settling in with the situation, and the level of information present in the family and the local pediatrician. Since this malformation is rare, most office-based pediatricians may see one affected child, if any, during their entire life as a practicing doctor. They can very rarely draw upon their own experience with this malformation and its implications.

Like in healthy children, the frequency and severity of bronchopulmonary infections are found to decrease as immunocompetence increases toward school age. But in many affected patients, the susceptibility to such infections persists into adulthood. This is due to bronchial dyskinesia and possibly tracheomalacia, which may entail secondary complications like scarring, emphysema, and bronchiectasis. A barky cough will accompany many patients into their adult years [44, 45, 47].

It is important to note that the esophagus is not a healthy organ after surgical correction. There will be impairment of esophageal motility and clearance in almost all cases, which may go unnoticed by the patients as they are used to it. These problems may be the underlying cause for GERD or respiratory disease developing beyond the patients' childhood and youth. Since swallowing problems are considered normal to some extent by many patients with EA repair, they may be late in noticing any deterioration. Late complications of anastomotic strictures or peptic stenosis include dilation of the prestenotic esophagus – and in the worst case diverticular pouch formation.

Without follow-up monitoring, EA patients may not become aware of GER or GERD for a long time. Due to the malformation and the dissection required for surgical repair, the function of the distal esophagus is poor. Acid reflux, therefore, may not cause discomfort or heartburn, and early Barrett's syndrome or peptic stenosis may go largely unnoticed.

It has been for a few decades only that medical progress has allowed patients with complications or long-gap atresia to survive and grow to reach

adulthood. Hence it is not yet possible to give an evaluated statement on the risk of complications that may occur after a very long period of time (>30 years). An increasing number of adolescents or adults present at PSOs with a first onset or recurrent history of swallowing disorders, GER, or changes of the esophageal mucous membrane. Investigations show that the esophageal mucosa has an increased risk of developing metaplasia and dysplasia [49]. There are case reports of esophageal carcinoma after EA repair in patients who are much younger than the average of patients who are usually affected by this cancer [32, 33, 50]. This underlines the necessity of lifelong aftercare. To date, it has not been possible to clarify the very long-term risk of esophagus substitution, of biliary reflux associated with dumping syndrome as a complication of fundoplication with or without pyloroplasty, or of reduced esophageal clearing with or without acid reflux [14, 25, 33, 51].

Advantages of Structured and Standardized Aftercare from the Patients' Point of View

Many of the typical complications and sequelae of EA develop slowly and subtly. This attributes particular significance to consistent aftercare. Even though patients may see no reason to complain about existing symptoms or their deterioration, because they have grown accustomed to their condition, specific questioning as part of the aftercare procedure may help to reveal complications and sequelae that require treatment. The use of structured and standardized checklists to achieve a complete inquiry into relevant symptoms will increase the confidence of the examiner as well as patient safety. This will allow even the less experienced examiner to identify problems, which require further investigation or treatment.

In the opinion of the PSO, patients and/or their families need early information that consistent and lifelong aftercare is necessary even if corrective surgery was successful. This will reassure the patients and families that everything will be done to discover complications at an early stage and avoid secondary lesions. Moreover, the family is not left alone after discharge from hospital.

Contribution of Patient Support Organizations to the Long-Term Care and Aftercare of Patients with Surgical Repair of Esophageal Atresia

It is the traditional approach of Patient Support Organizations to provide aid on the basis of their members' personal experience. Interlinking patients, education, information about support options in problems after EA repair, and counseling in questions of everyday life are the cornerstones of patient self-help.

Over the years of their existence, the PSOs have been able to accumulate "living competence," which can be shared by all people with an interest in EA. This accumulated experience is also integrated into guidelines for the diagnostics, treatment, and aftercare of EA and its complications [52].

On this basis the German PSO strives to provide active support and improved aftercare for patients with EA correction and their families. Further political activities are undertaken to increase the awareness for the need to implement qualified aftercare at experienced and specialized healthcare centers.

As yet, recommendations for the aftercare of EA patients in hospitals are not evidence based, but are built on doctors' assessments and experience. Advice ranges from "not necessary," "should problems occur," and "occasional follow-up evaluations in the first years of life" to "regular monitoring – possibly throughout life."

Any opinion as to which condition requires treatment and which condition can be treated has a subjective bias. This explains the importance of guidelines for systematic and structured aftercare, which makes sure that the examiner inquires about all symptoms of typical accompanying diseases and complications. That is the only way to ensure that no relevant questions are forgotten during the doctor-patient consultation.

Reviewing the patient records may be difficult in between the daily routine of a hospital. PSO experience shows that sometimes awareness of a patient's history is incomplete. A short survey of patients' medical history in addition to their follow-up documents proves helpful to all parties and facilitates communication between attending doctors.

The German PSO KEKS e.V. developed a three-part concept to support a lifelong standardized aftercare of patients with EA repair:

1. KEKS e.V. defined follow-up appointments and the scope of follow-up examinations. The PSO developed standardized and structured questionnaires facilitating complete inquiries into all symptoms of typical complications and sequelae. Since no evidence-based standards of aftercare are available yet, the scheduling and volume of aftercare as well as the design of questionnaires were based on the experience gathered in the PSO and that of the medical experts of the PSO scientific advisory board. Thus the Aftercare Folder issued by the German PSO offers a guideline for lifelong standardized aftercare.
2. The structures and standardized questionnaires make documentation of follow-up evaluations easier for patients and doctors and facilitate communication between doctors.
3. Recent publication revealing a lacking consensus about management of esophageal atresia at last in Europe underlines the advantages of a registry about therapies and sequelae [53]. Entering the data as documented in the questionnaires of the German Aftercare Folder into a multicenter database will make it possible to evaluate both aftercare and treatment concepts. The German PSO is working to set up a database of that type. Analysis of the data will help to continuously evaluate and optimize the aftercare concept. In addition, the observation of long-term outcomes achieved with different therapeutic regimens will contribute to identifying the best treatment options.

PSOs in other European countries also are committed to regular and standardized aftercare and documentation in support of patients with EA repair. The Dutch PSO "VOKS" provides a concept for patient-controlled documentation of patient history. The French PSO "AFAO" supports the reporting of data from follow-up evaluations to a reference center. The AFAO also contributed to the guideline for interdisciplinary aftercare issued by the HAS (Haute Autorité de Santé). Their recommendations for a follow-up strategy are largely identical with those given in the German Aftercare Folder.

All PSOs principally have identified the necessity of consistent and lifelong follow-up as an important objective. PSOs are committed to supporting and developing appropriate concepts and guidelines. Hence, beyond providing traditional patient support, PSOs may help to optimize the medical care of patients after esophageal atresia repair.

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Part XI

Acquired Esophageal Problems

Esophageal Injuries and Foreign Bodies

58

Filippo Torroni, Paola De Angelis, and Luigi Dall'Oglio

The ingestion of foreign bodies (FBs) is a frequent occurrence in children, especially in early childhood. The risk period is between 6 months and 6 years, with predominance in males. The maximum peak incidence is between 1 and 2 years of life when the age of exploration of their environment begins. The ingestion is almost always an accidental event (93 % of cases) – excepting patients with neurological deficit and psychiatric patients. Generally an FB passes through the digestive tract without causing damage – in children about 80 % of FBs ingested are eliminated spontaneously within a week [1, 2].

It is of extreme importance to verify the shape and chemical characteristics of the FB, as well as the impaction area. FBs smaller than 2 cm usually pass spontaneously into the stomach. FBs are categorized by size and considered large in diameter if ≥2 cm in children younger than 1 year or if ≥3 cm in children older than 1 year. These are less likely to progress beyond the stomach or may even stop in the middle third or the esophagus where it is compressed by the aortic arch – alternatively these may stop at the level of the lower esophageal sphincter or pylorus [3, 4].

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The symptoms are related to the location and to the typology of the FB: refusal to eat, dysphagia, odynophagia, chest pain, regurgitation, retching, and vomiting. Rarely stridor may occur in the case of arrest of an FB in the upper esophagus. Cough, laryngeal stridor, and cyanosis may occur in cases of laryngotracheal compression or inhalation. The different types of ingested FBs can be schematically listed, both on the basis of morphological categories and in relation to their potential hazard:

- Foods: meat boluses, large pips, bones (especially those of fish), cartilage
- Objects: harmless (e.g., coins or similar) or dangerous (pins, sticks, paper clips, long or bulky objects)
- Toxic containers (disk batteries, items containing lead, containers of drugs)

The radiological examination is a very important, and often decisive, step in the assessment of a patient with an ingested FB. A chest X-ray without contrast is generally sufficient to verify the presence and localization of a radiopaque FB. If radiopacity of the FB is questionable, it can be very useful to assess a twin object, when present. As radiolucent objects can escape first detection, the use of an adequate contrast can be useful. The X-ray examination should be performed erect, including the neck, the chest (anterior and lateral projection), and the abdomen. The radiological examination is also essential in the identification

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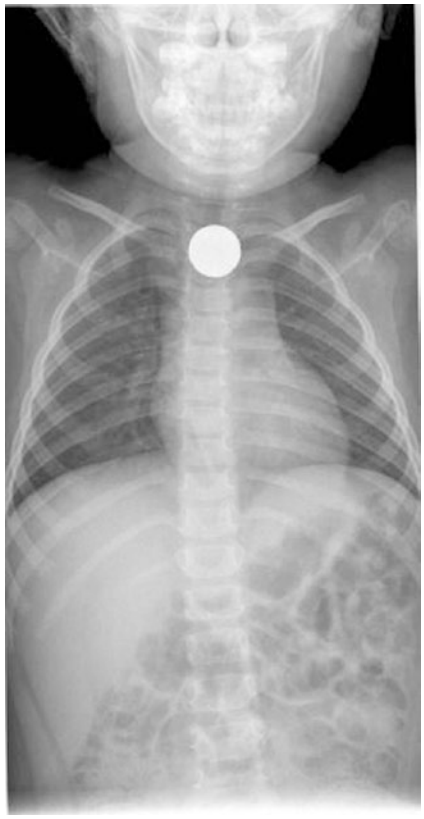

Fig. 58.1 Coin impacted in the cervical esophagus (cricopharyngeus muscle)

of possible complications, such as pneumomediastinum or pneumoperitoneum [5, 6].

The most frequent impact site described in literature is the cricopharyngeus muscle, while the middle part of the esophagus is the least frequent (Figs. 58.1 and 58.2). The patients who have esophageal abnormalities such as tracheoesophageal fistulae, previous surgery of esophageal atresia, and caustic ingestion are at risk of entrapment in atypical locations. Indication and timing of endoscopic removal in the management of pediatric patients who accidentally swallow an FB depend on many factors: the type of FB, the site in which the FB is trapped in, and the general conditions of the patient and the clinical picture. Management of the child with an esophageal coin has typically included an invasive coin removal procedure, usually endoscopy. Coins in the distal esophagus, however, often pass spontaneously into the stomach in the first 24 h after the

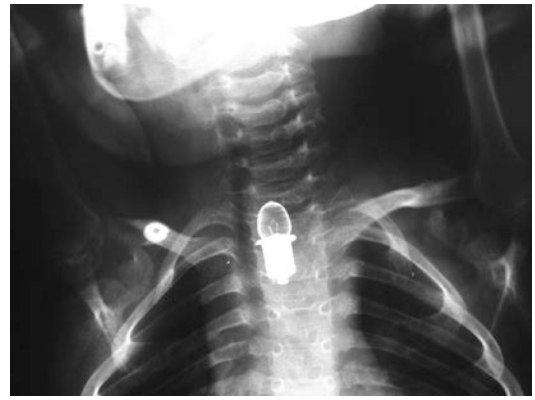

Fig. 58.2 Light bulb impacted in the cervical esophagus

ingestion, suggesting that conservative management alone may be effective. There is no agreement in the literature concerning the management of asymptomatic patients. In 2005 a prospective randomized trial which considered only asymptomatic and risk-free patients with esophageal coin localization demonstrated a good probability (about 30 %) of spontaneous passage toward the gastric cavity [7, 8].

In the literature, foreign bodies are most often fish bones, metal objects such as batteries and coins, and fragments of broken tooth [9]. Tissue response depends on the composition of the FB and also any associated bacterial infection. Organic fragments can cause an acute inflammation greater than those caused by pieces of metal, plastic, or bone. Button batteries are particularly dangerous for children – the frequency of ingested button batteries is about ten per million population per year. Battery ingestion causes serious injuries, and hence immediate endoscopic removal of esophageal batteries is warranted, i.e., an endoscopic emergency. The mechanism of injury that occurs includes direct corrosive action due to leakage, toxic effect due to absorption of substances, low-voltage burns, and necrosis. Necrosis, and perforation, can occur in 4–6 h after a disk battery is lodged in the esophagus, while tracheoesophageal fistula and esophageal stricture/stenosis within 10 h have been described [10–12] (Figs. 58.3 and 58.4). There have been reports of tracheoesophageal fistulae and Meckel's diverticulum perforation secondary to

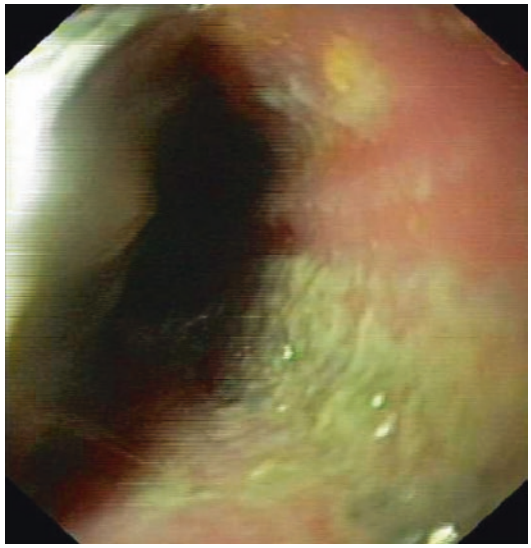

Fig. 58.3 Disk battery impacted in the esophagus

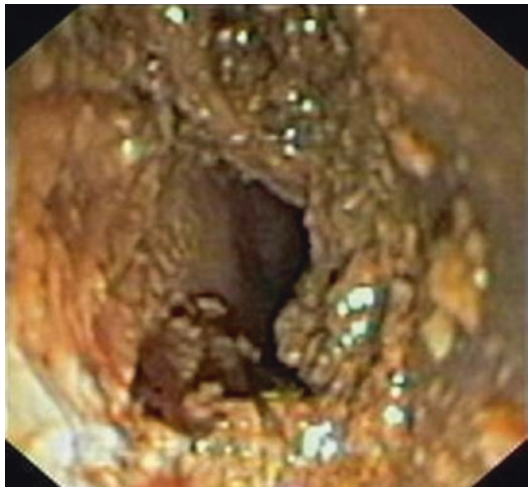

Fig. 58.4 Disk battery ingestion: esophageal injuries (necrosis)

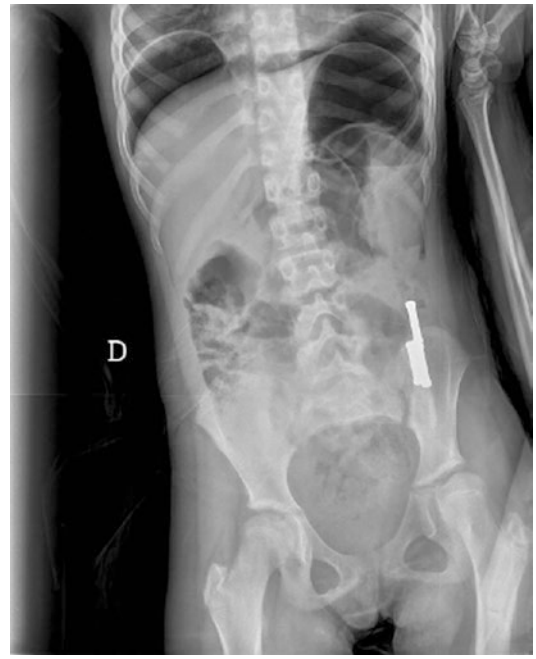

Fig. 58.5 Abdominal X-ray: two magnetic objects lying in different intestinal loops with intestinal perforation

disk battery ingestion [13, 14]. Endoscopic emergency is the gold standard for all complicated situations or high risk, particularly for sharp and pointed foreign bodies, such as dentures with protruding hooks, razor blades, and open safety pins, which increase the risk of perforation. Esophageal lesions are particularly dangerous because of the proximity to major vessels and organs including the heart. The ingestion of magnets is a frequent occurrence in children. Singly ingested magnets do not cause specific problems and have to be considered as not dangerous foreign bodies. Two or more magnetic objects lying in different intestinal loops may produce a considerable attraction force with consequent crushing and fistulization between intestinal lumen. Severe damage such as ulceration, fistulae, hemorrhage, and perforation can occur [15–17] (Fig. 58.5).

In one pediatric patient who had had endoscopic removal of a foreign body in the lower esophagus, a few months after removing the foreign body, persistence of dysphagia was observed. An X-ray examination with contrast was performed and revealed an esophageal diverticulum (Fig. 58.6). The common wall was cut with a precut needle knife (*Boston Scientific*®), resulting in patency between the diverticulum and the esophageal lumen (Fig. 58.7).

In approximately 95 % of cases, underlying esophageal pathology contributes to impaction – such as peptic injuries, previous caustic ingestion, and postoperative strictures or stenosis. Eosinophilic esophagitis (EE) represents another

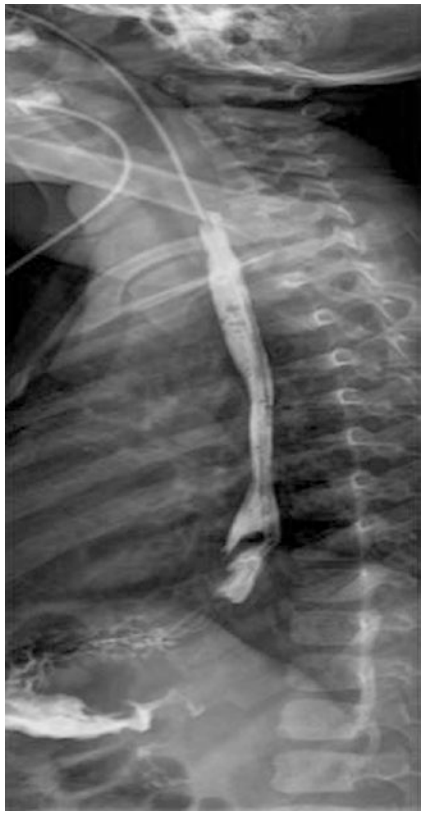

Fig. 58.6 X-ray examination with contrast: esophageal diverticulum

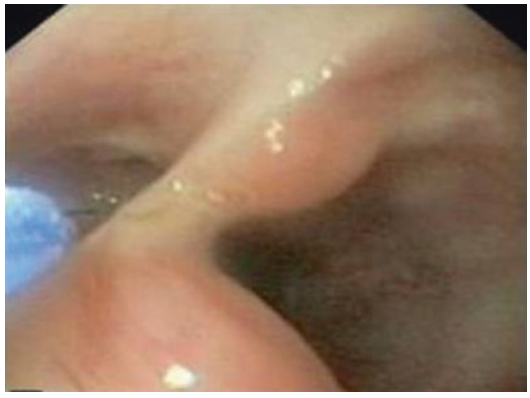

Fig. 58.7 Endoscopic image: esophageal diverticulum

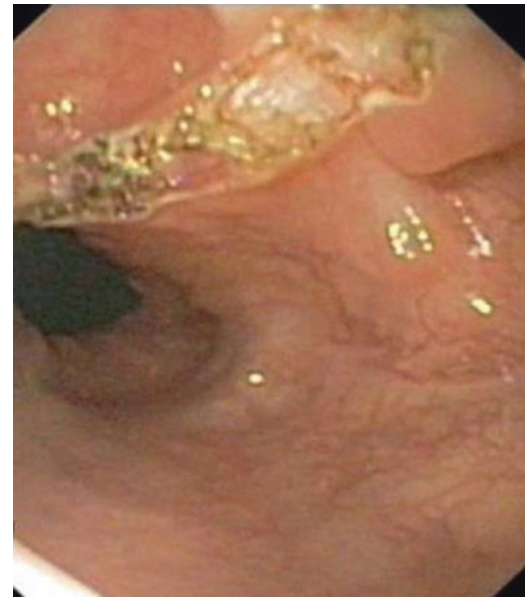

Fig. 58.8 Esophageal diverticulum: section of the common wall

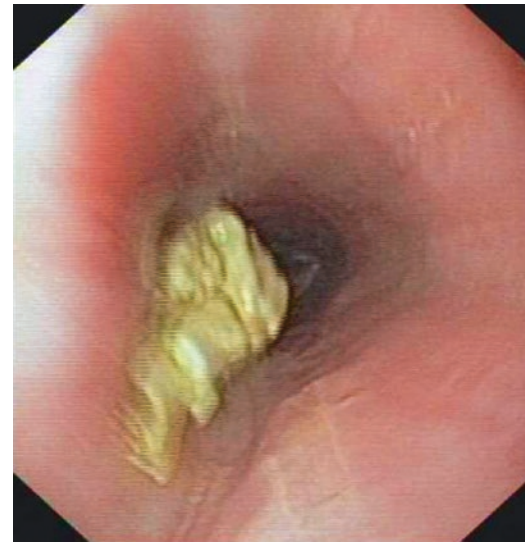

Fig. 58.9 Esophageal food impaction

common pathology recognized more recently (Fig. 58.8) [18]. Typical features include circular rings – "trachealization," white specks, linear furrowing, and associated motility disorders (Fig. 58.9). It would seem that the natural evolution of this disease at a mucosal level is toward stricture (Fig. 58.10).

In congenital stenoses a preliminary radiological assessment is useful to exclude the presence of bony fragments or cartilage. Endo-ultrasound (EUS) can be helpful.

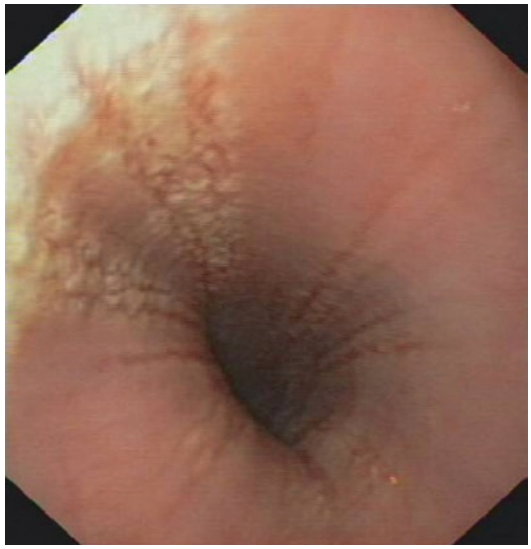

Fig. 58.10 Eosinophilic esophagitis

Recourse to the surgeon becomes mandatory in cases where it is necessary to solve an unexpected situation or an unexpected complication at the time of endoscopic removal or in cases where foreign bodies are too large or potentially harmful to predict a complete and safe endoscopic removal [19]. The literature contains a significant number of observations regarding serious consequences resulting from the ingestion of two or more magnetic elements, able to attract also through distant segments of the alimentary canal leading to intestinal perforation. In the situation of multiple ingestions, removal must be quick [20, 21].

It is important to highlight the concept of known malformations of the digestive tract or situations that may determine difficulty in gastrointestinal transit.

In summary, FB ingestion may compromise the esophagus and lead to stricture formation, but importantly the ingestion of batteries and magnets merits the most urgent endoscopic examination.

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Caustic Ingestions

59

Mário César Vieira
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Introduction

Caustic injury to the digestive tract remains a significant medical concern despite efforts to minimize the hazards of caustic household products in various countries. The ingestion may be harmless or it may have severe effects, and there are divergent opinions on how to diagnose and treat pediatric patients who ingest caustic agents.

Epidemiology

Corrosive ingestion is a widespread problem in many parts of the world. In the United States, a decline in the incidence of caustic injuries has been observed, but despite all the new laws and precautions, there is an incidence of approximately 5,000–15,000 cases per year [1]. Nevertheless, an increase has been reported in other countries such as Turkey and India [2, 3]. In developed countries, alkaline material accounts for most cases of caustic ingestion, whereas acid ingestion may be more common in some developing countries, like India, where sulfuric acid and hydrochloric acid are easily accessible [4].

The ingestion of caustic agents occurs most commonly accidentally in children less than 6 years of age and especially in those between 12 and 48 months. Although children in this age group account for 51 % of toxic exposures, they account for only 2.3 % of fatalities (fatality rate of 0.0022 %) primarily due to low-volume ingestion of caustic agents [5, 6]. This is in distinction to ingestions in adolescents and adults, the majority of which are deliberate as part of a suicide attempt. The significantly higher fatality rate in adolescents and adults results from the different outcomes associated with an intentional ingestion of a high volume, and high concentration, of a caustic or other poisonous products [6]. A concept of "accidental-deliberate" ingestion was proposed by Betalli et al. referring to the well-recognized situation where the child drinks a high volume of caustic substance which is contained in a bottle of apparently drinkable fluid, e.g., juice or mineral water, unaware of its content [7].

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A number of studies tried to assess the importance of the educational level of parents, as well as social economic aspects that could be related to the incidence of caustic ingestion in children. Turkish investigators studied families of 50 children that ingested caustic material and 60 controls using a questionnaire, which included sociodemographic data and questions about their knowledge, attitude, and behavior toward corrosive ingestion. The level of education of both mothers and fathers in the corrosive group was lower than that of the controls. Families in the corrosive group had three or more children (42 %), and the socioeconomic status of this group was lower than the controls. In the corrosive group, these substances were purchased unlabeled (64 %) and kept mainly in soft drink bottles. The authors concluded that both level of education of parents and socioeconomic factors play an important role in predisposing to corrosive ingestion in children [8].

Etiology

A variety of substances are responsible for caustic injuries ranging from alkaline agents with pH greater than or equal to 12, to acidic substances with pH as low as 2, as well as bleaching substances where the pH is around 7 (Table 59.1).

High concentrations of alkali are found in lye-based (NaOH, KOH) agents as drain and oven cleaners, dishwashing detergents, as well as cosmetics which may be freely accessible to children in the home environment. Unfortunately, these products may not be perceived by families as a potential hazard due to their ubiquitous nature and lack of childproof packaging.

Granular forms of caustic substances are associated with a higher rate of injury in comparison with liquid forms because of their potential for localized contact. Crystalline alkali drain cleaners may result in deep injury due to adherence in areas of anatomic narrowing [3, 9, 10].

Button batteries, containing high concentrations of sodium and potassium hydroxide, can also cause severe injuries.

Acids are available in battery fluids (sulfuric), toilet bowel cleansers (sulfuric, hydrochloric), antirust compounds (hydrochloric, oxalic), and swimming pool cleansers (hydrochloric) [3, 10].

Milder injuries are usually caused by sodium carbonate, ammonium hydroxide, and bleaches (sodium and calcium hypochlorite and hydrogen peroxide). Bleaches are relatively pH neutral and are seldom associated with severe injury.

Legislation to reduce the concentrations of various household caustics and childproof packaging are not in place in many countries, and therefore injury following unintentional ingestion

Table 59.1 Common caustic substances

Caustic substance	Type	Commercial product
Alkali	Sodium hydroxide Potassium hydroxide sodium carbonate	Drain cleaner Oven cleaners Soap manufacturing Washing products Disc batteries Drying fruit on farms
Acids	Sulfuric Oxalic Hypochloric phosphoric	Batteries Paint thinner, toilet cleaner Solvent Metal cleaner
Detergents/bleach	Sodium hypochlorite Sodium polyphosphate	Household bleach Industrial detergent
Condy's crystals	Potassium permanganate	Hair dye Disinfectant
Ammonia	Ammonium hydroxide	Household cleaners

may be more frequent and severe in such places [5]. The use of "non-original" containers such as juice or soft drink bottles to store cleaning products increases the risk of accidental ingestion substantially.

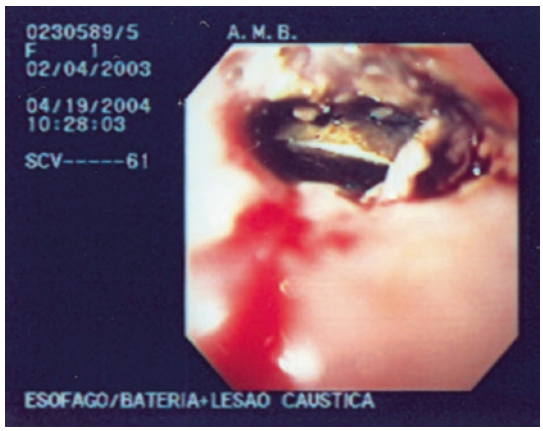
Mechanisms of Injury

The pathogenesis of injury varies among different products [11]. Acids cause coagulation necrosis, which results in a self-limiting burn pattern with the formation of a somewhat protective coagulum layer at the site of injury. Acids are more often associated with gastric injury, with less extensive injuries to the esophagus. Their specific gravity and viscosity are lower than liquid alkalis resulting in rapid transit to the stomach and leading to injuries especially in the prepyloric area and even in the duodenum. Their noxious taste and pungent odor may limit the amount ingested. Gastric injury following ingestion may result in gastric outlet obstruction or perforation frequently in the area of the gastric antrum or pylorus [12]. Chlorine bleaches are considered irritants only and are less likely to cause severe pediatric injury.

Disc batteries found in watches, toys, remote controls, and hearing aids among other places can become impacted in the esophagus with subsequent leakage of alkaline material around its seal. These contain high concentrations of KOH or NaOH and can cause damage if they remain in the esophagus even for brief periods (Figs. 59.1 and 59.2).

Alkalis induce liquefaction necrosis with saponification of fats, solubilization of proteins, and deep diffusion of the substance into the tissues with more extensive and deeper burns. Only neutralization of the substance by the tissue itself will cease the reaction. Because of increased tissue adherence, alkalis also cause more damage to the esophagus; however, deliberate ingestion of large quantities of alkali may injure the stomach and even the small intestine. The initial contact of the agent will produce immediate and progressive changes in the mucosa. The injury evolves in three phases: acute phase (minutes to 72 h) with intense inflammatory reaction that causes erythema and edema of the superficial layers associated with necrosis, bacterial infiltration, and vascular thrombosis; subacute phase (3 days to 3 weeks) with ongoing inflammation, granulation tissue formation, and collagen formation; and chronic phase (>3 weeks) in which vigorous collagen deposition by fibroblasts results in thickening and scarring of the wall. Stricturing is the end result of cicatrization.

The severity and extent of injury depend on multiple factors, such as the volume ingested, the concentration of the agent, duration of contact with mucosal surfaces, and pH of the solution (damage is greatest when the pH is >12). Solid



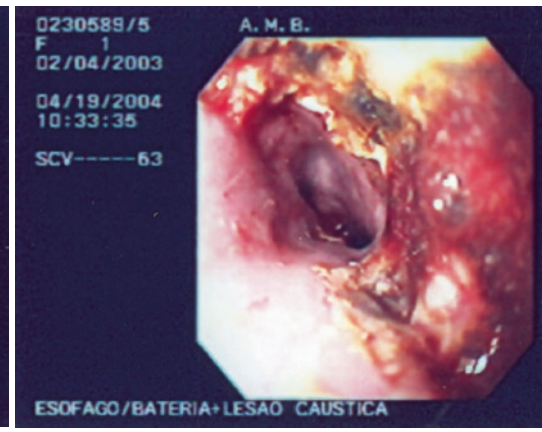


Fig. 59.1 and 59.2 Caustic injury caused by a button battery lodged in the esophagus for 6 h

preparations and viscous liquids produce more severe injury owing to a longer contact time with the oral mucosa. The amount ingested is usually limited by the pain experienced by the child upon accidental exposure but even small quantities can cause significant lesions. A correlation between the depth of lesion and the concentration of sodium hydroxide (NaOH) solution has been shown in animal experiments. When a solution of 3.8 % contacts the esophagus for 10 s, it produces necrosis of the mucosa and submucosa. A 10 % solution extends the injury to the muscular layers of the esophagus. Transmural injury occurs with a few seconds of exposure to a 22.5 % NaOH solution [3, 5, 9, 12].

Clinical Manifestations

After the ingestion of a caustic agent, patients can present from having few symptoms to a frankly toxic state with evidence of visceral perforation.

A burning pain in the mouth and substernal or epigastric areas with swelling of the lips may occur. The most common symptoms are dysphagia, excessive salivation, feeding refusal, and vomiting. These symptoms may develop rapidly or be delayed for several hours and usually last days to weeks.

Symptoms involving the airway are less common and include hoarseness, stridor, and dyspnea, and if there is perforation, a shock-like picture may occur.

Despite this, guidance of treatment by signs and symptoms is not always adequate. Several studies have shown that signs and/or symptoms do not adequately predict the presence or severity of a pediatric lesion although an increased number of symptoms correlate with a greater likelihood of significant injury [3, 13]. In a Turkish study of 473 pediatric caustic ingestions, primarily of alkaline agents, 240/389 (61 %) children without oral burns had lesions found at endoscopy. In that study, 80 % of patients had an esophageal injury and 17 % of patients had gastric injury [14]. In a review of 378 pediatric caustic ingestions, 12 % of asymptomatic patients had severe esophageal burns, whereas 82 % of symptomatic patients had no esophageal injury [15]. Other series have also demonstrated the discordance between oral and esophageal burns [3].

Emergency Management

An adequate initial management is directed at maintaining an adequate airway and ensuring cardiovascular stability and depends on accurate diagnosis. Very often the causative agent is unknown, and a careful history detailing the time, modality of ingestion, type, brand name, and amount of ingestion of the substance should be obtained. Asking the parent to bring the original product container may help to identify the chemical properties of the agent that can influence the severity of gastrointestinal lesions. It is also important to know whether vomiting occurred as this can increase the length of time of esophageal exposure.

Most children do not present any symptoms and do not have any lesion because the caustic has not really been ingested but only tasted. Patients may be asymptomatic, but may also have varied signs and symptoms. They may present with burns on the lips, chin, chest, and hands. There may be burns in the mouth and pharynx, which should be examined with proper lighting. It is essential to bear in mind that signs and symptoms are not always reliable as some patients with moderate-to-severe esophageal injury can have few of these complaints [5, 10, 13].

Inducing emesis and gastric lavage should not be encouraged as this determines a risk of further injury on reexposure of the esophagus to the caustic agent. Neutralization of alkali with vinegar and sodium bicarbonate for acids is inappropriate because an exothermic reaction may result in further damage to the tissue [16].

Analgesics are indicated for patient comfort. There is no clear evidence of a direct effect of medical treatment on the prevention of strictures [17].

Some advocate that the placement of a nasogastric tube can be useful in severe esophageal injuries to avoid stricture formation by preventing luminal adherence. This can be placed with caution in the first 24 h either under fluoroscopic guidance or at

the time of endoscopy. In their usage in 32 patients with severe circumferential burns, Wijburg et al. had stricture development in only two patients [18]. Nevertheless it is essential to bear in mind that there is a risk of perforation and that vomiting may be induced with the passage of the tube.

Protection of burned esophageal mucosa from gastric acid reflux is generally considered important although not proven in human studies. H_2 blockers or proton pump inhibitors and sucralfate may help prevent further esophageal damage [3, 10, 19, 20].

Different investigators have demonstrated the effectiveness of the use of corticosteroids in reducing the inflammatory response, fibrous tissue proliferation, and stricture formation, particularly in grade 2 injuries [21, 22].

A prospective randomized study over an 18-year period, involving 60 children with pediatric caustic injury, concluded that steroids are not beneficial in preventing strictures in children after caustic ingestion [23]. A meta-analysis of studies between 1991 and 2004 and an analysis of the literature on corticosteroid use between 1956 and 2006 also failed to demonstrate a benefit of steroid administration in terms of stricture prevention [24, 25]. Despite the absence of conclusive data, when steroids are used, treatment must be started within the first 8 h for maximal effectiveness in case of grade II lesions [26]. In third-degree burns, steroid use may be contraindicated because of a theoretical higher risk of developing perforations, although this risk has not been well documented. Dexamethasone (1 mg/kg/day) appears to be more effective than prednisone (2 mg/kg/day) [27]. Further prospective studies are needed in order to demonstrate the efficacy of the steroids in changing the natural history and reducing the risk of stricture.

Antibiotic use is controversial in the treatment of serious injuries. Theoretically, decreasing bacterial counts in the burned tissue would lead to a reduction in granulation tissue formation with less chance of stricture formation. Others would argue that antibiotics may mask the signs of more serious infection. If prophylactic antibiotics are used, third-generation cephalosporins or ampicillin at 50–100 mg/kg/day is recommended [3, 10, 17].

A radiographic exam of the neck, chest, and abdomen is indicated especially if any symptom of respiratory distress or visceral perforation is suspected. Contrast radiographic study is of little use in the acute phase since it only delays endoscopy and may not reveal first- or second-degree damage.

The role of biochemical markers of injury is not certain, although some parameters such as neutrophilic leukocytosis and metabolic acidosis can give an indication of the severity of clinical condition [28]. Metabolic acidosis (pH <7.22), arising mainly from tissue necrosis, may indicate serious damage with poor prognosis [28, 29]. Different biochemical abnormalities have been studied in acute caustic ingestion in an attempt to identify markers of injury. Otçu et al. conducted a prospective study in 78 children with caustic ingestion performing an extensive biochemical analysis, blood gas estimations, chest radiography, and endoscopy. Blood pH level was decreased in patients who ingested household bleach but did not differ in patients with or without injury. These authors identified increased levels of uric acid and decreased levels of phosphate and alkaline phosphatase in patients with caustic lesions of the esophagus [30].

Recently, a grading system using computed tomography (CT) was proposed as a useful noninvasive modality on a retrospective study of 49 patients with caustic ingestion. The authors found CT to be as effective as endoscopic findings in order to estimate the occurrence of complications including esophageal stricture suggesting that this diagnostic method could be useful particularly in cases in which larger doses of caustics were ingested, vital signs were unstable, or an early stage endoscopy could not be performed [31].

Endoscopy

Routine evaluation by endoscopy after caustic substance ingestion is still a matter of debate particularly in asymptomatic patients [7, 32, 33]. However, endoscopy may prove to be particularly valuable in the event of large amounts of

substance ingested, attempted suicide, or persistent symptoms.

Since signs and symptoms are not accurately predictive of esophageal damage, a routine upper gastrointestinal endoscopy is traditionally recommended by most authors on suspicion of caustic ingestion, except for asymptomatic children in whom the ingestion is dubious. Nevertheless, there are no strict guidelines as to when endoscopy is indicated and on how much to advance with the endoscope.

The procedure should only be done by an experienced endoscopist. Flexible endoscopy has made this procedure safer, once perforations are more likely to occur with rigid instruments. In the severely affected patient, maintenance of airway to prevent obstruction as well as hemodynamic stabilization may be crucial, and abdominal and chest radiographies should be taken to detect perforation or pulmonary complications. Some authors suggest that, based on endoscopic findings, one can individualize the management preventing unnecessary treatment or allowing early intervention when there is a serious case [3, 7].

A classification system for mucosal damage was proposed in 1989 and latter modified by Zargar et al. in order to standardize the description of injuries (Table 59.2) [34]. Patients with minor (grade 1) or no esophageal injuries would be discharged once they are able to take oral fluids. Those with more extensive injuries (grades 2 and 3) would be given intensive hospital care. Grade 2a (superficial, non-circumferential) lesions rarely progress to esophageal stricture although some patients may require dilation. Grade 2b and 3 lesions are associated with an increased risk of stricture formation [3, 7, 34]. In general it is suggested that endoscopy is carried out within 24–48 h (some authors recommend 72 h) of ingestion for better demarcation of the degree of injury. After this period, there may be an increased chance of iatrogenic perforation due to structural weakness in the esophageal wall. Some authors recommend to terminate the endoscopy at the level of the most proximal circumferential burn to avoid perforation, and others advocate that a full examination of the esophagus, stomach, and duodenum should be performed [5, 17, 21, 28, 35, 36].

On the other hand, there are some researchers who are against early esophagoscopy because of the risk of esophageal perforation. A retrospective study evaluating the need for early endoscopy in 124 adult patients who have ingested a corrosive agent showed that early endoscopy appears to be unnecessary in adult patients who ingested the corrosive agent accidentally. Based on their findings, these authors state that the most important point in patients who had ingested a caustic agent is to detect whether there is a perforation in the acute stage. They suggest that after ruling out perforation, radiography with water-soluble, nonionic contrast material may be performed for the assessment of the severity of esophageal and stomach burns. If there is no perforation, a treatment should be planned for a stricture that may develop in the future [19].

Another recent prospective study involved 350 children with a history of caustic ingestion where no patient underwent an early endoscopy and were followed up for at least 24 h in hospital. Patients tolerating oral feeding well were discharged with advice on progression in symptoms and deterioration in vital signs to be observed over a 48–72-h follow-up. A contrast study of the upper gastrointestinal tract was performed in all patients with persistent dysphagia within 3 weeks after injury. In case of a stricture, a dilatation program was initiated. These authors state that, in practice, the endoscopic findings do not bring useful data to change the modality of treatment and that it would lead to unnecessary general anesthesia and possible com-

Table 59.2 Zargar's classification of mucosal caustic injuries [34]

Grade 0	Normal
Grade 1	Mucosal edema and erythema
Grade 2a	Superficial ulceration, erosions, friability, blisters, exudates, hemorrhages, whitish membranes
Grade 2b	Grade 2a plus deep discrete or circumferential ulcerations
Grade 3a	Small scattered areas of multiple ulceration and areas of necrosis with brown-black or grayish discoloration
Grade 3b	Extensive necrosis

plications associated with the procedure at the most fragile period of esophageal damage [37].

Based on these data and on the absence of proven therapy to prevent stricture, the recommendation of early endoscopy in patients with caustic ingestion still remains an issue of controversy. Large prospective studies with clearly defined protocols are needed to resolve this question.

Late Management

Stricture Dilatation

Despite adequate early management, when healing is occurring, stricture formation is the major complication following caustic ingestion in 10–40 % of esophageal burns depending on the grade of the initial injury [7, 36]. Because the contractile phase of the healing process begins around 2 weeks after injury, in the majority of cases, the strictures develop within 2–8 weeks after the ingestion [5].

Endoscopic dilatation is required as a primary treatment for esophageal strictures and should always be undertaken slowly and carefully, as a planned procedure where possible, in patients who have been adequately prepared with previous clinical and radiological assessment.

Dilation is accomplished by application of expansible forces against a luminal stricture. Dilation devices can be organized into two categories: fixed-diameter push-type dilators and radial expanding balloon dilators [38]. Fixed-diameter push-type dilators exert axial as well as radial forces as they are advanced through a stricture. Balloon dilators exert radial forces when expanded which is thought to be less likely to result in a tear of the esophagus than the other methods. Despite these mechanistic differences, no clear advantage of either balloon or bougie (Savary-Gilliard) dilation has been demonstrated [39–42].

Dilators can be placed at the stricture site in different ways, based on the dilator design and operator experience, including with or without endoscopic, fluoroscopic, and/or wire guidance. Fixed-diameter and balloon dilator devices include through-the-scope (TTS) and non-TTS types. Through-the-scope dilators must be placed by the endoscope accessory channel. Most push-type dilators are non-TTS devices and are introduced over a guidewire which is initially positioned under endoscopy followed by subsequent endoscope removal. Both anterograde and retrograde esophageal dilation are widely used in different centers. Push dilators may be mercury filled (Maloney), solid (Jackson), or wire guided (metal olives, Celestin-type bougies, or polyvinyl dilators). Eder-Puestow dilators comprise a series of graduated metal olives (6.6–19.3 mm diameter) mounted on a flexible shaft. In the past it was the only system available for dilating resistant or complicated strictures. The system is believed to be useful in patients with tortuous strictures or small stomachs. Retrograde dilation is felt to be safer by some and was originally described by Tucker. In this method, a continuous loop of string is kept in the esophageal lumen and brought out of the nose superiorly and a gastrostomy inferiorly. A Tucker dilator is tied to the lower end of string and pushed and pulled out of the patient's mouth [43].

Polyvinyl dilators have become more widely used in recent years. Savary-type dilators consist of a range of flexible taper-tipped polyvinyl chloride cylinders (5–20 mm diameter) with a central channel for passage over a guidewire. Savary-Gilliard dilators (Wilson-Cook Medical Inc., Winston-Salem, NC) have a long tapered tip and a radiopaque band at the widest point for radiological localization. The American Dilation System dilators (C. R. Bard, Inc., Billerica, Mass.) are similar but dilators have a shorter taper tip and are radiopaque throughout their length [40].

Balloon dilators may also be used and may be passed through the scope or be wire guided. They are positioned at the narrowest part of the stricture under direct view and then inflated with water to a pressure that corresponds to a specific diameter. The principal disadvantage of balloon dilators is their cost.

Both Savary-Gilliard and balloon dilators are currently by far the most frequently used dilators, but these need to change to esophageal balloons as soon as possible [38, 40].

The efficacy and safety of endoscopic dilation without fluoroscopy have been shown in several studies [44, 45]. However, it is generally recommended to use fluoroscopic guidance to enhance safety during dilation of complex strictures [38].

Frequency and timing are individualized and based on symptoms, nutritional status, and general health conditions. Dilatations may be performed at weekly or fortnightly intervals with a very gradual increase in dilator size. The need for repeated dilatations is based on clinical judgment until the maintenance of adequate nutritional status with appropriate swallowing and normal oral feeding can be established. The period of dilatation may be extended over months or years with progressively longer intervals between procedures. Patients should be closely observed following the procedure in order to identify symptoms and signs of possible iatrogenic perforation as a result of therapeutic dilatations. Most perforations occur in complex strictures that have been dilated without fluoroscopic guidance.

If a patient develops pain, breathlessness, fever, or tachycardia, perforation should be suspected and chest radiography should be performed urgently. The consequences of perforation may be significant and include pneumothorax, pneumomediastinum, need for esophageal or gastric surgery, or death. Minor perforations have been treated with intravenous nutrition and antibiotics without surgery and resumption of dilation in 4–8 weeks [46–48].

Many patients with caustic esophageal strictures have GERD due to motility changes and to the shortening of the esophagus [49, 50]. Although there are no clinical studies to document the effectiveness of the use of anti-reflux medication, this treatment is recommended empirically in reducing stricture formation. The use of sucralfate to coat and protect the esophageal ulceration may be also recommended empirically especially after dilatations.

Stenting

The development of self-expanding and removable plastic stents (Polyflex®) may be promising in reducing the number of dilatation sessions and keeping the patency of the esophageal lumen for longer periods. Broto et al. conducted the largest experiment in pediatrics, in which ten patients with esophageal strictures unresponsive to endoscopic dilatation were submitted to esophageal stenting, with good results [51]. Recently, the use of a biodegradable esophageal stent in a child was reported with a favorable outcome [52].

Steroids

Intralesional triamcinolone (TAC) injections may reduce the risk of recurrent stricture formation in patients with corrosive esophageal stricture [53]. Although the steroid injection seems to be superior over regular dilatation, this needs to be determined by controlled studies. In addition, it remains to be defined what the optimal injection technique and frequency are and at what dose triamcinolone should be injected.

Mitomycin C

Mitomycin C is an antifibrotic agent derived from the Actinobacteria *Streptomyces*, which acts by interfering with RNA synthesis, thus inhibiting fibroblast proliferation and consequent reduction in the amount of scar formation. Local application of mitomycin C may be performed by using different endoscopic techniques. A cotton pledget held by endoscopic forceps and soaked in a 0.1 mg/ml solution of mitomycin C can be applied topically under direct vision, either using an overtube or a standard cap used for band ligation of varices attached to the end of the endoscope, the agent from touching the normal mucosa [54–56]. A recent report has described the use of injections at the site of stricture with promising results [57]. The ideal concentration, duration, or frequency of application is unclear.

Although there is a theoretical increased secondary long-term risk of malignancy associated with the use of mitomycin C and there is a need for controlled trials confirming its efficacy, this substance should be considered as a promising

adjunct in the management of esophageal strictures in children.

Surgery

Failure to respond to dilatation is an indication for esophageal replacement [58]. Colonic interpositions, jejunal interpositions, and gastric pull-ups are options. However, the definition of "failure" is not clear when deciding to perform a replacement surgery [37, 59]. As other colleagues we believe esophageal replacement in caustic strictures should be exceptional. These are extensive surgical procedures, and scarring often remains a problem, with strictures most commonly occurring at the cervical anastomosis.

Surveillance for Esophageal Cancer

An important consideration relates to the 1,000-fold increased risk of esophageal carcinoma (both adenocarcinoma and squamous cell carcinoma) with a latency period of 15–40 years in patients with histories of caustic ingestion. This association is supported by the location of the cancer at the site of the stricture and the younger age of patients with caustic ingestion-related carcinomas [3, 10, 60]. Dysplasia screening is recommended for patients following a severe caustic ingestion to allow for the early detection of premalignant changes. Guidelines from the American Society for Gastrointestinal Endoscopy in 2006 recommend that endoscopic surveillance should begin 15 years after ingestion, with endoscopy performed every 1–3 years [61].

Psychosocial Implications

An important part of management is continuous support to the child's parents and other caregivers at the time of injury. Manifestations of anxiety or even aggression reflecting a sense of blame or guilt are common at initial presentation. Long-term psychosocial impact may include the development of educational problems, such as school avoidance, antisocial behavior, and feeding difficulties even after successful dilatation. There may be a higher risk of family breakups and abandonment often associated with financial implications and parental absenteeism from work [10, 21].

The involvement of a clinical psychologist is important to help the child as well as the family in coping with the long-term psychosocial consequences of caustic ingestion.

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Esophagitis: Causes Other Than Reflux

60

Mike Thomson

Inflammatory processes in the pediatric esophagus have received a disproportionately small amount of attention until recently, when appreciation of their pathophysiology and concordant clinical importance has been highlighted. This increase in interest and exposure is probably a phenomenon secondary to a number of important factors, which include improved diagnostic yield from relatively recent technical advances in areas such as infant and pediatric endoscopy; advances in fields such as mucosal immunology, allowing for the realization that etiopathologic mechanisms for esophagitis are more complex than simple luminal chemical damage; and a shift in clinical opinion recognizing esophageal pathology as a major cause of nonspecific ubiquitous symptoms such as infant colic, feeding disorders, and recurrent abdominal pain among others. A state of knowledge such as this has made pediatric esophagitis, until recently, a relatively underdeveloped area of research and clinical understanding, but this is rapidly changing [1].

It is now clear, therefore, that esophagitis in infants and children has many responsible etiologic pathways that may have complex interactions and hence requires equally complex diagnostic and therapeutic strategies. Such causative factors are now known to include cow's milk protein (CMP) intolerance or allergy, pH-dependent and pH-independent gastroesophageal reflux (GER), dysmotility of various causes, and infective, traumatic, and iatrogenic causes, among others. Hence, the term "esophagitis" can be used to describe chemical, infectious, inflammatory, ischemic, immunologic, and degenerative abnormalities [2]. Nevertheless, there remains a minor degree of controversy regarding the definition and significance of esophagitis, as assessed by the standard diagnostic techniques, including endoscopy and biopsy [3, 4]. This chapter attempts to describe basic etiologies other than reflux-related esophagitis and does not deal with eosinophilic esophagitis which is dealt with in subsequent chapters.

Etiology and Pathophysiology

The etiologies of esophagitis in infancy and childhood can usefully be divided into the following groups:

1. Chemical:
   (a) Owing to refluxed contents from the stomach and duodenum such as gastric acid, pepsin, bile, and trypsin
   (b) Owing to swallowed substances, either intended such as medications or accidental caustic ingestion such as dishwasher liquid

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2. Immunologic: owing to specific responses to specific antigens such as CMP or multiple food intolerance or allergy
3. Infective: associated with organisms as diverse as *Helicobacter pylori* (with associated reflux), *Candida*, cryptosporidiosis, herpes simplex, and *Cytomegalovirus* (CMV)
4. Traumatic: secondary to intraluminal trauma (e.g., long-term nasogastric tube) or irradiation (e.g., as part of bone marrow transplant conditioning)
5. Systemic disease manifestation: associated with conditions such as Crohn's disease and chronic granulomatous disease
6. Miscellaneous: such as that associated with passive smoking or that occurring in fictitious or induced illness (Munchausen syndrome by proxy)
7. Idiopathic: eosinophilic esophagitis

The etiopathologic role of each of these situations can therefore be usefully discussed under each heading, bearing in mind that an individual child or infant may, of course, have more than one factor contributing to the esophageal insult at any one time (e.g., GER and cow's milk-associated esophagitis).

Chemical

Chemical esophagitis owing to swallowed substances.

Ingested materials are usually household or garden substances and are usually markedly alkaline; the common one was dishwasher fluid, often with a pH of 9 or above. However, fortunately, in most countries, this has been replaced with powder, which is less easy to swallow, and even individually wrapped tablets of powder. Acute perforation, mediastinitis, and subsequent esophageal stricture have frequently been seen. The possibility of non-accidental injury should not be forgotten in this context. It is notable that the rate of subsequent stricture formation is high, and more recently, a potentially effective post-dilation topical application of an anti-fibrotic, mitomycin C, has shown promise in preventing restenosis and long-term repeated stricture dilation [5].

Restenosis post-dilation of strictures due to many variable pathologies has now been successfully prevented by the use of this substance applied topically at endoscopy – the only pathology which may be refractory to its effect is in epidermolysis bullosa [6] (Fig. 60.1).

Many medications have been associated with esophageal damage and symptoms of esophagitis, and these include tetracyclines (not recommended under the age of 12 years, of course), drugs used in acne therapy, and nonsteroidal anti-inflammatory drugs [7–10].

Immunologic

Although it is now clear that multiple food antigens may induce esophagitis [11, 12], the most common precipitant is CMP. Standard endoscopic biopsy and histology do not reliably distinguish between primary reflux esophagitis and the emerging clinical entity of cow's milk-associated reflux esophagitis. This variant of cow's milk allergy appears to be a particularly common manifestation in infancy, with symptoms indistinguishable from primary GER but that settle on an exclusion diet [13]. Some dif-

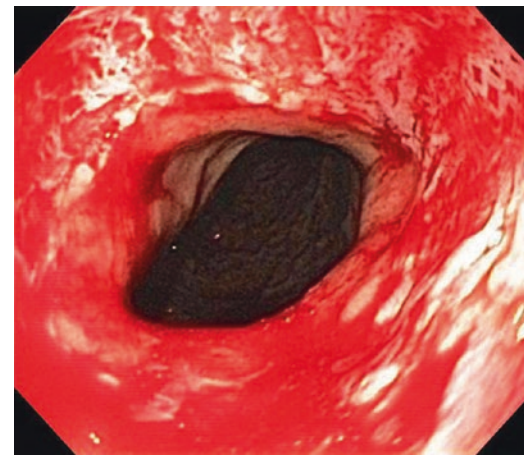

Fig. 60.1 Example of caustic injury to the esophagus

ferentiation from primary reflux has been suggested on the basis of an esophageal pH testing pattern and an α-lactoglobulin antibody response, although the former has not been substantiated by more than one center [13, 14]. There is recent evidence that this esophagitis is becoming a more common presentation of infant food allergy within the developed world and, in fact, may be induced by a variety of antigens in addition to cow's milk [11, 12]. Many affected infants have sensitized while exclusively breastfed, and a defect in oral tolerance for low doses has been postulated as the underlying cause [15, 16].

Esophageal mucosal eosinophilia has been described in both suspected cow's milk-associated [11] and primary reflux esophagitis (Fig. 60.2) [17], as well as in other conditions, such as idiopathic eosinophilic esophagitis (EE) [18]. A variety of immunohistochemical markers have been used to examine the esophageal mucosa, including eotaxin, a recently described eosinophil-specific chemokine (Fig. 60.3) [19], and markers of T-cell lineage and activation. Despite the mild histologic abnormality in CMP-associated esophagitis, an increased expression of eotaxin co-localized with activated T lymphocytes to the basal and papillary epithelium has been shown [20], distinguishing this from primary reflux esophagitis. The molecular basis of the eotaxin upregulation in cow's milk protein-sensitive enteropathy (CMPSE) is unknown. However, there is evidence from murine models of asthma that antigen-specific upregulation of eotaxin expression can be induced by T cells and blocked by anti-CD3 monoclonal antibodies. This suggests the possibility of a distinct mechanism in CMPSE, in which mucosal homing to the esophagus occurs of lymphocytes activated within the small intestine. This may explain the seemingly counterintuitive finding of the basal, as opposed to superficial, chemokine expression, and the common occurrence of mucosal eosinophilia in this condition. The esophageal motility disturbance of CMPSE-associated esophagitis is thus suggested to occur as a neurologic consequence of the inflammatory infiltration induced from lamina propria vessels into the epithelial compartment [21]. This proposed mechanism contrasts with the current concept of luminally induced inflammation found in primary reflux esophagitis and is consistent with the characteristic delayed onset and chronic nature of cow's milk-associated reflux esophagitis. It has also been suggested that increased numbers of mucosal mast cells allow a distinction to be made between allergy-induced and reflux-induced esophagitis [22]. Much work is required in this area and is ongoing.

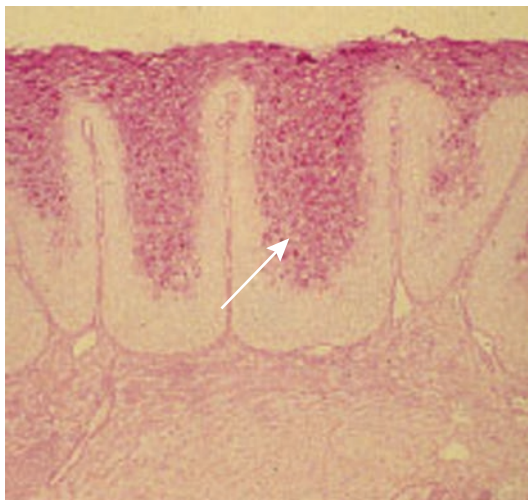

Fig. 60.2 Esophageal mucosal eosinophilia seen in cow's milk-associated and primary reflux esophagitis and primary eosinophilic esophagitis. (Eosinophils marked by *arrows*)

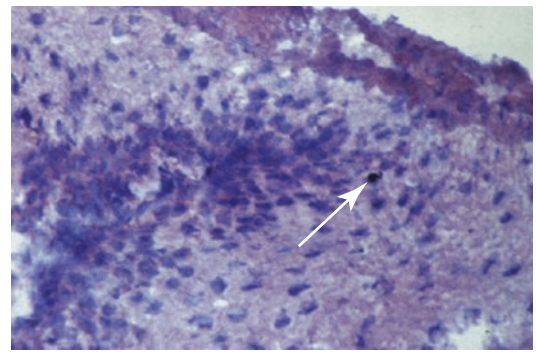

Fig. 60.3 Eotaxin, a recently described eosinophil-specific chemokine. (Darker staining area marked by an *arrow)*

Infective

The majority of infective esophagitis that occurs is in the immunocompromised child and is due to such agents as herpes simplex, CMV, *Candida*, and others. Mucosal damage owing to physical or chemical causes may predispose the patient to opportunistic infection. Oral herpes or *Candida* may offer some clue to etiology, and the older child will often complain of odynophagia or dysphagia. Diagnosis may be made on endoscopy with biopsy, but brushings may offer a greater diagnostic yield.

Viral esophagitis is usually due to herpes simplex, CMV, and, occasionally, *Varicella zoster* [23–25]. Herpes simplex esophagitis can occur in those with normal immune function [26], but is more often seen in those who are immunocompromised. In one series, 10% of the liver or kidney transplant recipients had herpes or CMV esophagitis [27], and it is also commonly seen in pediatric human immunodeficiency virus (HIV) infection [28]. The use of prophylactic acyclovir/ganciclovir is conjectural but may be of some benefit.

The diagnosis of herpes esophagitis is often difficult because the characteristic nuclear inclusions and multinucleate giant cells may not be seen in endoscopic biopsies; however, a prominent mononuclear cell infiltrate is described as characteristic (Fig. 60.4) [29]. It may be that the esophagus is particularly vulnerable in the GI tract owing to affinity of the herpes virus for stratified epithelium. Typically, roundish distinct disseminated lesions with yellowish borders are seen and have been termed "volcano ulcers" (Fig. 60.5) [30] although early in the presentation, vesicles may be noted. Although the inflammation can resolve spontaneously in the immunocompetent, in those with poor immune function, acyclovir and a high index of suspicion are recommended [30]. Resistance to acyclovir has been described, in which case, foscarnet is the agent of choice [31]. CMV esophagitis is confirmed by basophilic nuclear inclusions on biopsy of the edge of the ulcers, which are similar in appearance to herpetic ones. CMV is predominantly found in immunocompromised individuals, and treatment is with ganciclovir or foscarnet [25]. Hemorrhage, fistulae, and esophageal perforation in adults with viral esophagitis are described [32, 33]. Acute HIV infection can also cause esophagitis [34].

Candida, the most common infectious cause of esophagitis, has the classic appearance of white plaques on the mucosa, which cannot be washed or brushed off, unlike food or milk residue, and which often extends up to the upper

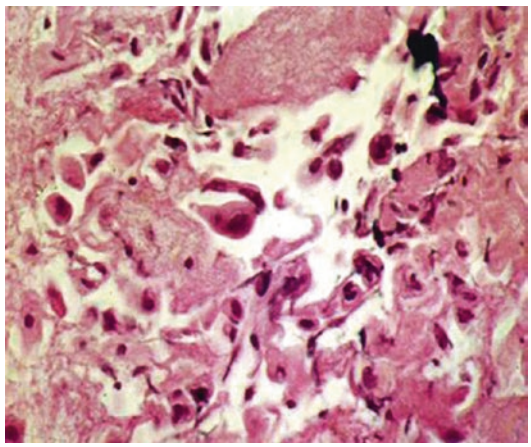

Fig. 60.4 Herpes esophagitis with nuclear inclusions, multinucleate giant cells, and a prominent mononuclear cell infiltrate

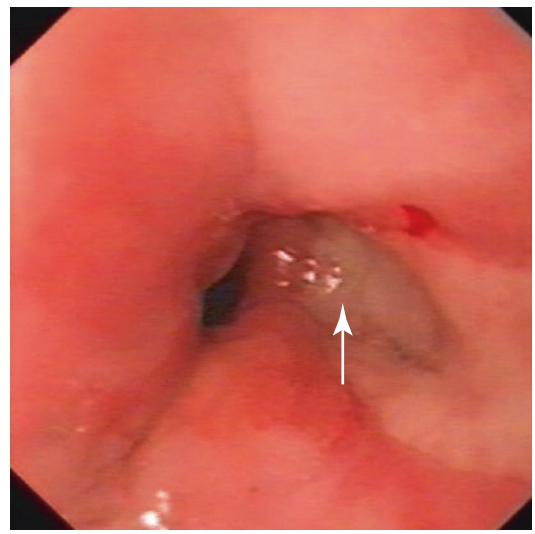

Fig. 60.5 Macroscopic appearances of herpes esophagitis. Roundish distinct disseminated lesions with yellowish borders are seen and have been termed "volcano ulcers" (*arrow*)

third of the esophagus (Fig. 60.6) [35]. Oral *Candida* is not predictive of esophageal involvement except in the immunocompromised host, but even in these children, extensive esophageal involvement is seen in the absence of oral candidiasis [36]. Mucositis and a white cell count less than 0.5×10^6/L predispose patients with leukemia to candidal esophagitis [37]. Steroid use (even poor technique with inhaled steroids for asthma) or acquired or congenital immunocompromise may be etiologic and may have the appearance of white focal lesions on the esophageal surface (Fig. 60.7). This appearance may be difficult to distinguish from eosinophilic esophagitis. Apart from the macroscopic appearances, diagnosis is confirmed by the presence of hyphae in biopsies (Fig. 60.8). Culture is not helpful because coexistent oral *Candida* can confuse the assessment. Complications include fistulae, perforation, painless stricture formation, esophageal dysmotility, transient achalasia [38], and systemic candidiasis. A 2–6 week course of oral nystatin can be effective in those with normal immune function, but it is more convenient to give fluconazole. Fluconazole or liposomal amphotericin is required, and both are effective in the immunocompromised child. Esophageal resection and diversion for necrotizing candidal esophagitis have been successful in a 10-year-old [39].

Eradication of *H. pylori* in adults has been associated with increased acid production and hence more noxious gastroesophageal refluxate. However, there does not seem to be any increased incidence of esophagitis in the presence of, or following, the eradication of *H. pylori* in children [40]. Because *H. pylori* affects gastric epithelium, it is not surprising that it has been identified in Barrett epithelium in a child, in whom symptoms

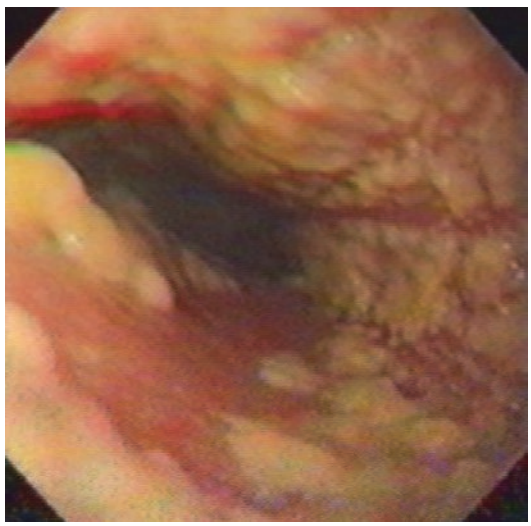

Fig. 60.6 Candidal esophagitis has the classic appearance of white plaques on the mucosa that cannot be washed or brushed off

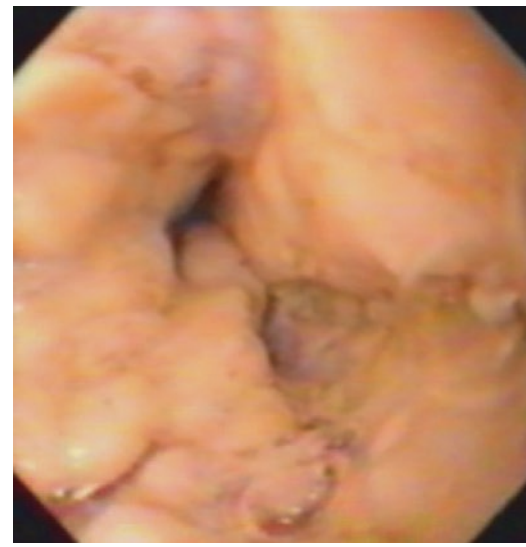

Fig. 60.7 Candidal esophagitis may have the appearance of white focal lesions on the esophagus, which may be difficult to distinguish from allergic esophagitis

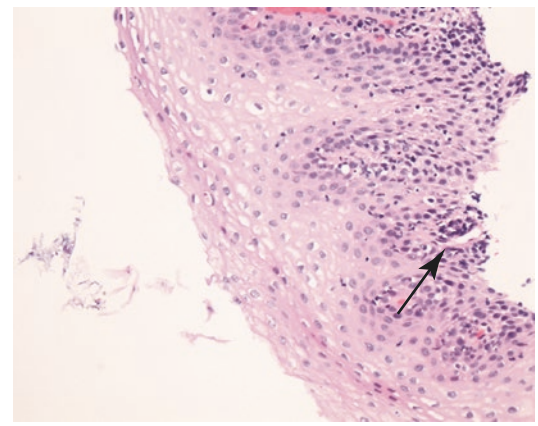

Fig. 60.8 Candidal hyphae (*arrows*)

resolved only with addition of amoxicillin to anti-reflux therapy [41]. Primary bacterial esophagitis is described in immunocompromised patients and may be successfully treated with long-term ciprofloxacin, metronidazole, or penicillin – or a combination dependent on bacteria and sensitivity [42].

Other opportunistic organisms causing esophagitis, such as *Cryptosporidium* and *Acremonium*, have been reported [43, 44].

Traumatic

Trauma causing esophageal pathology could, of course, be accidental, intentional, or iatrogenic. The presence of a nasogastric tube may be associated with abrasive esophagitis, and it has been postulated that the severe esophagitis found in newborn infants in one study, in the absence of other etiologic factors, may have been secondary to enthusiastic upper GI suction at birth [45]. Of particular note was the severity of the esophagitis in the face of relatively minimal symptomatology, such as feeding refusal. Radiation-induced esophageal strictures are described in children receiving mediastinal irradiation (usually greater than 4,000 cGy) and doxorubicin, occurring between 1 and 10 years post-therapy [46]. Radiation-associated esophagitis following bone marrow transplant conditioning is known to occur in the subsequent 1–2 weeks but is usually amenable to medical therapy.

Systemic Disease Manifestation

GER occurs more commonly in diverse conditions such as cystic fibrosis, severe combined immunodeficiency, cerebral palsy, raised intracranial pressure, celiac disease, and conditions associated with impaired gastric emptying [47, 48]. Certain diseases are, however, associated with esophagitis, which is not via the pathogenetic pathway of reflux. Crohn's disease is a prime example, and Crohn's lesions in the esophagus are usually distinct rounded ulcers, although diffuse disease may also occur (Fig. 60.9). Endoscopic examination with biopsy of the upper GI tract should be part of the diagnostic workup of a child with suspected Crohn's disease [49]. Relapse of the disease may be associated with recurrence of esophageal manifestations [50]. Type 1b glycogen storage disease may present with similar phenotype to Crohn's disease, and severe esophageal involvement has been noted in childhood in this condition [51]. Inflammation and stricturing of the esophagus can occur in chronic granulomatous disease and can involve most of its length, making balloon dilation difficult [52]. Scleroderma and vasculitic conditions such as polyarteritis nodosa have significant esophageal pathology in adults but are very rare in pediatric populations. Graft-versus-host disease may present in the esophagus although this is less likely than other GI areas such as the stomach and rectum. Epidermolysis bullosa is a debilitating disease that may also involve the esophagus, as are other dermatological conditions which affect the esophagus such as lichen sclerosus et atrophicus.

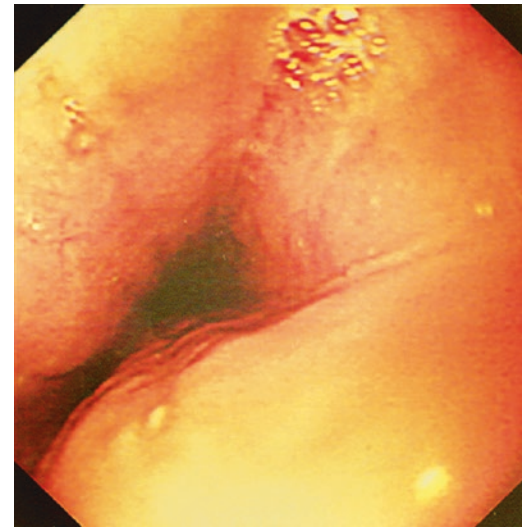

Fig. 60.9 Distinct round ulcers of Crohn's esophagitis

Miscellaneous

Passive smoking has a strong association with esophagitis in childhood. The reasons behind this are not completely understood, but nicotine is

known to relax the LES and may decrease mucosal blood flow. The nicotine levels in swallowed saliva may directly injure the esophagus or render it more susceptible to injury from acid exposure. Also, free radicals present in tobacco smoke may reduce antioxidant defenses [53].

Fictitious or induced illness (Munchausen syndrome by proxy) can be at the root of esophagitis in children, but this is usually due to the deliberate introduction into the esophagus by the perpetrator of caustic or irritative substances [54].

Idiopathic: Eosinophilic

Eosinophilic esophagitis (EE) is the subject of a subsequent chapter.

Management and Prognosis

Management of esophagitis must, of course, be dictated by its etiology, which further underlines the vital nature of obtaining an accurate diagnosis based on upper endoscopy and histologic assessment.

Because the vast majority of cases of esophagitis in infants and children will be due to GER, then treatment of GER and treatment of GER-related esophagitis will be very closely linked. Treatment of GER is also dealt with in other chapters. Other specific treatments for specific pathologies are also dealt with.

Infective causes of esophagitis in pediatrics require specific therapies. Viral esophagitis is usually due to herpes simplex, CMV, and, occasionally, *Varicella zoster* [23–25]. Although the inflammation can resolve spontaneously in the immunocompetent, in those with poor immune function, acyclovir and a high index of suspicion are recommended [30]. The use of prophylactic acyclovir is conjectural but may be of some benefit posttransplant. Resistance to acyclovir has been described, in which case, foscarnet is the agent of choice [31]. CMV esophagitis is predominantly found in immunocompromised individuals, and treatment is with ganciclovir or foscarnet [25]. Hemorrhage, fistulae, and esophageal perforation in adults with viral esophagitis have been described [32, 33].

Acute HIV infection can also cause esophagitis, and antiretroviral regimens are needed [34].

Candida is the most common infectious cause of esophagitis. A 2- to 6-week course of oral nystatin can be effective in those with normal immune function, but it is more convenient to give fluconazole. Fluconazole and liposomal amphotericin are both effective and are necessary in the immunocompromised child.

Eradication of *H. pylori* is not likely to improve coexistent esophagitis, and, indeed, in adults, eradication has been associated with increased acid production and hence more noxious gastroesophageal refluxate. However, there does not seem to be any increased incidence of esophagitis in the presence of or following the eradication of *H. pylori* in children [40]. Primary bacterial esophagitis is described in immunocompromised patients and requires appropriate antibiotics dictated by sensitivity testing [42]. Other opportunistic organisms causing esophagitis, such as *Cryptosporidium* and *Acremonium*, have been reported and require appropriate therapy [43, 44].

Treatment of caustic esophagitis is initially conservative, with barium swallow at 4–6 weeks post-ingestion, endoscopic assessment, and, if necessary, stricture dilation. The place of steroids in stricture prevention is controversial and not routine in many centers. Recently, the use of an anti-fibrotic, mitomycin C, applied topically to the mucosa post-stricture dilation has been used successfully in patients who have required multiple stricture dilations, with prevention of restenosis (Fig. 60.1) [5]. Antibiotic therapy for mediastinitis and judicious use of surgery may be employed.

Older children whose esophageal stratified epithelium is exposed to long-term acid may, as with adults, develop gastric metaplasia, eponymously termed Barrett's esophagus [55–57]. This increases the lifelong risk for esophageal adenocarcinoma approximately 30- to 40-fold. Debate surrounds the relative merits and success rates of anti-reflux surgery or long-

term proton pump inhibitor use, and this is dealt with in greater detail elsewhere in the book.

Prognostication in infant and childhood esophagitis is wholly dependent on etiology, however, fortunately, the most common causes, reflux and allergy, are relatively self-limiting, with a natural improvement and recovery by 18 months to 2 years in the vast majority. This is dealt with in greater detail at the beginning of the section on treatment. It is the responsibility of the pediatrician to prevent avoidable complications such as peptic strictures occurring during the period of vulnerability until such an age has been reached. A low threshold for diagnosis and intervention is therefore sensible in this population.

Treatment of EE is dealt with in detail in a seperate chapter.

In summary, pediatric esophagitis is no longer regarded as a unidimensional reflux-related condition, and the main reason cited by the recent conjoint ESPGHAN-NASPGHAN working group on reflux and esophagitis for endoscopic assessment in this group of patients is diagnostic differentiation of reflux esophagitis from other conditions such as eosinophilic esophagitis and other inflammatory and infective etiologies [58]. The developments in physiologically appropriate tools such as impedance and the rapid rise in comprehension of issues such as neurohumoral interactions controlling esophageal function, combined with the recent apparent explosion in incidence of new esophageal diseases in children – for example, eosinophilic esophagitis – suggest that the study and clinical care of children with esophageal inflammatory disorders are likely to be of expanding interest to the pediatric gastroenterology community as each year goes by.

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Eosinophilic Esophagitis (North America)

61

Aileen Har and Sandeep K. Gupta

Introduction

Eosinophils are involved in and mediate a variety of disease processes including parasitic and fungal infection, allergic reactions, hematologic malignancies, autoimmune diathesis, and endocrine disorders [97]. Eosinophils can also be part of normal/baseline histological makeup of certain organs. For example, in the gastrointestinal tract, there is a variation in the eosinophil load in the healthy state where a relatively high number of eosinophils are present in the cecum, but are strikingly absent in the healthy esophageal epithelium.

Eosinophilic esophagitis (EoE) involves eosinophilic infiltration restricted to the esophagus without evidence of gastroesophageal reflux (GER) [28]. Eosinophilic infiltration is limited to the esophageal epithelium with concomitant epithelial changes such as vascular papillae elongation and basal cell hyperplasia [71]. This entity had been sporadically reported in the literature with limited attention until 1995 when Kelly et al. published a series of 12 children who had significant eosinophilic inflammation of the esophagus that was unresponsive to standard anti-reflux therapy including six children who had underwent Nissen fundoplication [43]. Patients with EoE may present with a variety of symptoms, several of which may be similar to gastroesophageal reflux disease (GERD) including regurgitation, nausea, feeding intolerance, and epigastric pain. Others may present with more specific symptoms such as dramatic and recurrent dysphagia and food impactions. The diagnosis of EoE has increased in recent years, which may be due to both increased recognition of the disease and actual increase in incidence [11, 48, 67, 95].

As of now, our understanding of EoE is still in its infancy with much to be discovered in this relatively new entity. This chapter will discuss the pathogenesis, epidemiology, diagnosis, treatment, and long-term outcomes of EoE.

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Other Causes of Eosinophilia in the Esophagus

While eosinophils are present in the healthy state in most parts of the gastrointestinal tract, they do not normally reside in the healthy esophagus [79]. Other than EoE, there are a variety of conditions that may lead to eosinophilic infiltrate of the esophagus with the most common being GER (Table 61.1) [17]. In GERD, exposure of the esophageal epithelium to gastric contents containing pepsin, trypsin, and gastric acid results in nonspecific inflammatory infiltrate with involvement of a variety of cytokines and chemokines, along with other inflammatory mediators [20]. While the exact pathways involved are not completely understood, it is postulated that the direct exposure of esophageal epithelial cells to gastric contents causes secretion of pro-inflammatory mediators as well as activation of mesenchymal and endothelial cells leading to an upregulated immune response [76]. A mixed infiltrate consisting of neutrophils, eosinophils, mast cells, and macrophages is seen in the esophageal epithelium of patients with GERD, but the degree of eosinophilia is generally less than that seen in EoE and is usually limited to the distal esophagus.

Fungal infections of the esophagus are more common in the setting of immunocompromise, broad-spectrum antibiotic use, inhaled corticosteroid usage with improper technique, malignancy, or chronic metabolic disease [13]. *Candida sp*. are the most frequently isolated fungal organisms from the esophagus. Patients most commonly present with dysphagia or odynophagia and may have abdominal pain, globus sensation, nausea, vomiting, dyspepsia, and in severe cases upper gastrointestinal bleeding. The endoscopic picture of esophageal candidiasis can be similar to that of EoE with adherent white plaques, though the plaques with candidiasis are of a "cheese-like" appearance. Histology and fungal brushings are useful to differentiate between the two conditions as hyphae can be identified in candidiasis.

Table 61.1 Causes of esophageal eosinophilia

Gastroesophageal reflux disease
Eosinophilic esophagitis
Infection – parasitic and fungal
Connective tissue disease
Eosinophilic gastroenteritis
Hypereosinophilic syndrome
Inflammatory bowel disease/Crohn disease
Drug-induced injury

Connective tissue diseases such as scleroderma intrinsically cause an elevation of eosinophils in the esophagus due to generalized inflammation. Systemic scleroderma affects the esophagus in 75–90 % of patients [15] leading to dysmotility and abnormal functioning of the lower esophageal sphincter thereby causing a predisposition to GERD with further increase in inflammation.

Other inflammatory conditions where there is recruitment of eosinophils to the esophagus include injury due to medications. Pill esophagitis occurs when there is prolonged contact of medication with the esophageal surface. Medication-induced esophagitis has been reported with nonsteroidal anti-inflammatory drugs, alendronate, quinidine, tetracycline, doxycycline, potassium chloride, ferrous sulfate, and mexiletine with higher risk in patients with esophageal dysmotility and decreased salivation [30]. Large or sustained release pills as well as ingestion in the supine position or ingestion with insufficient water predisposes to injury. Endoscopy may reveal erythema, erosions, and/or ulcerations; strictures or perforation could be seen with severe cases.

Eosinophilic gastroenteritis typically involves the stomach and small bowel, but may expand to the esophagus or colon [106]. It is a rare condition and even less common in the pediatric age group with the typical presentation in the 30–50-year age range [31]. Eosinophilic inflammation may be limited to the mucosa and submucosa or may involve the muscle layers to the extent of full-thickness inflammation [52]. Clinical presentation is varied and depends on the location and depth of tissue inflammation; symptoms can include diarrhea, abdominal pain, weight loss, failure to thrive, protein losing enteropathy, iron

deficiency anemia, and eosinophilic ascites [27]. These patients may have a history of atopy and peripheral eosinophilia. The pathophysiology is unclear, but in infants, the trigger may be milk-protein intolerance, and in older children, there may be associated IgE-mediated hypersensitivity to food [42].

Hypereosinophilic syndrome (HES) comprises of sustained peripheral eosinophilia >1,500 eosinophils/mm^3 for 6 months, absence of other eosinophilic syndromes or identifiable etiology for eosinophilia, and end-organ involvement [14]. HES is a group of heterogeneous syndromes with a male predominance of 9:1, and age of diagnosis ranged from 20 to 50 years [103]. Organ systems that may be affected include cardiovascular, dermatologic, pulmonary, gastrointestinal, and ocular. Gastrointestinal involvement can include esophagitis, gastroenteritis, and colitis as well as hepatitis and Budd-Chiari syndrome.

Pathogenesis

The exact molecular mechanisms underlying eosinophilic infiltration of the esophageal epithelium are poorly understood and remain incompletely defined. The infiltration in EoE is thought to be secondary to an allergic process, and patients with EoE have an increase in overall genetic dysregulation with an elevation of eosinophil-directed cytokine expression in the esophagus [8, 34, 91]. There is a noted increase in T cells and mast cells [46, 54] within the esophageal epithelium as well as an upregulation of interleukin (IL)-5, IL-13, interferon (IFN)-γ, and tumor necrosis factor(TNF)-α production that does not involve the stomach, duodenum, or peripheral circulation [34, 91]. T-helper 2 (Th2) cell-associated cytokines have been implicated in the recruitment of eosinophils to the esophagus.

A genetic variant of the eotaxin-3 gene, an eosinophil-specific chemoattractant, also known as CCL26, may predispose to development of EoE [8]. Patients with histological diagnosis of EoE have a highly conserved esophageal transcriptome seen on genome-wide transcription analysis of biopsy specimens. The highest induced transcript in EoE patients is reported to be eotaxin-3, and its induction is not seen in patients with chronic esophagitis due to other causes or in healthy individuals. In fact, esophageal transcriptomes of non-EoE esophagitis patients were similar to that of those without esophagitis. Eotaxin-3 levels correlated with EoE disease severity and were expressed in EoE patients with and without known food or aeroallergies. Deletion of the eotaxin-3 receptor, CCR3, in mouse models has been shown to be protective of EoE development [60, 61]. In vitro experiments on esophageal tissue treated with IL-13 induced production of CCL11 and CCL26 at levels sufficient to cause eosinophil migration [64].

Epidemiology

EoE has been described in both pediatric aged and adult patients. The mean age of diagnosis in children is 8.6 years with a range of 0.5–21.1 years, and there is a striking gender bias to EoE with two thirds of patients being male [28]. Epidemiologic data is wanting, but limited studies indicate an incidence around 1:10,000 yearly and prevalence is estimated around 1:2000 [11, 48, 67, 95]. Several centers, including those in the United States, have noted a steady increase in yearly diagnosis of EoE [87]. It is unclear if incidence of EoE is truly increasing or if it is partially due to increased recognition. EoE has been described throughout most of the world except Africa, but there is a lack of data looking at ethnic predilection. There may be a familial preponderance for the disease, but it is unclear if the link is genetic vs. environmental exposure [59, 72, 95]. Up to 8 % of patients with EoE have parents with esophageal biopsies consistent with EoE, and 10 % of the parents have a history of esophageal strictures [67]. Fifty to 80 % of patients with EoE may have a personal and/or family history of atopy [50, 70]. There is evidence showing a seasonal variation in diagnosis, which may differ depending on the geographical location and the type or level of aeroallergens [24, 62, 74]. A published case involving a 21-year-old female

diagnosed with EoE showed clear variation of symptoms and histology correlating with spring and winter months [24]. Springtime and grass pollen counts also correlated with EoE diagnosis in a single center involving 127 patients – 33 % of diagnoses were made in spring and 16 % in winter [62]. In another study, 68 % of cases of EoE were diagnosed in spring/summer versus 27 % in winter [3].

Table 61.2 Presenting symptoms of EoE

Infants	Failure to thrive
	Feeding difficulties
	Gastroesophageal reflux symptoms
	Vomiting
School age	Abdominal pain
	Gastroesophageal reflux symptoms
	Vomiting
Adolescence	Dysphagia
	Food impaction

Diagnosis

EoE is defined as presence of ≥15 eosinophils in at least one high-power field (hpf) on esophageal mucosal biopsies, clinical symptoms of esophageal dysfunction, and absence of GERD as evidenced by persistent inflammation on high-dose PPI or normal 24-h continuous intraesophageal pH monitoring (pH probe) [28]. The most specific variables for diagnosis of EoE are loss of mucosal vascular pattern and vertical furrows in the esophageal mucosa on esophagogastroduodenoscopy (EGD); patients with improved symptoms on either an elemental diet or swallowed fluticasone are 160 times more likely to have EoE than GERD [48].

History and Physical Examination Presenting symptoms in the pediatric population vary by age. Patients with EoE can be difficult to recognize, and the time to diagnosis may range from 13 to 60 months from symptom onset [22]. Younger patients tend to present with feeding intolerance, refusal to feed, and failure to thrive, while children who present when they are older may have emesis, regurgitation, heartburn, and abdominal pain. As they enter adolescence, patients tend to have symptoms similar to adults – recurrent dysphagia and food impaction (Table 61.2). In a retrospective study of pediatric patients with follow-up period of over 10 years, 82 % of the patients presented with GER symptoms and only 18 % presented with dysphagia [50]. The presence of dysphagia and anorexia/early satiety may help differentiate patients with EoE from those with GER alone [2]. There is a dissociation between severity of symptoms and histological severity in the pediatric population making it difficult to predict histological findings based on symptoms alone [73]. Atopy, the tendency for an individual to have an IgE-mediated response to allergens resulting in asthma, atopic dermatitis, or allergic rhinitis, is found in 50–80 % of children with EoE [38, 50, 85]. In addition to personal history of atopy, patients have a family history of atopy and EoE at 43 % and 12 %, respectively [50]. The physical examination for EoE is nonspecific, but eczema or other signs of allergy may be elicited as may those of failure to thrive. Clinical evaluation of EoE is further challenged by coping mechanisms utilized by patients, and efforts to uncover these should be part of the evaluation. Coping mechanisms most commonly seen are texture avoidance/preference, excessive use of liquids at mealtime to assist passage of food bolus, excessive chewing of food, very small bites of food, and prolonged mealtimes.

Laboratory Data and Biomarkers Currently there is no ideal biomarker that accurately predicts the diagnosis, severity, remission, and relapse of EoE. Identification of a biomarker that could substitute for endoscopic examination and histological assessment would be exceedingly beneficial to both patients and health-care provider as it would substantially reduce the time and costs associated with repeated endoscopic procedures. The ideal biomarker would be sensitive, be specific, be reproducible, correlate with EoE state, connect with severity of disease, reflect changes caused by therapy, be obtained from specimens that are easily and noninvasively collected, and be cost-effective [33]. Potential

biomarkers for EoE include mast cell products, peripheral blood eosinophils, cytokines and chemokines, serum IgE and CD 23 levels, and eosinophil granular proteins such as eosinophil-derived neurotoxin (EDN).

The role of mast cells, and their products including leukotrienes and histamine, in the pathogenesis of EoE has yet to be conclusively delineated [39, 83, 100]. Leukotriene levels in esophageal mucosa in children with and without EoE are similar to those seen in controls [35]. N-methylhistamine, a stable metabolite of histamine which can be measured in urine, has been evaluated in inflammatory bowel disease, but not yet in EoE [104].

Mild peripheral eosinophilia (600–1,600 cells/μL) [97] is seen in 20–100 % of children with EoE [23, 45, 66, 70, 80, 98, 102]. The level of peripheral eosinophilia may decrease once treatment for EoE is initiated, but there is insufficient evidence to use it as a surrogate marker of disease activity [23, 47]. Patients may have an elevated total IgE level, but it is unclear if this is related to underlying atopy or specifically to EoE itself [51]. CD23 is a membrane protein that serves as an IgE receptor and is present on various cells including enterocytes and eosinophils. CD23 expression is induced by cytokines involved in allergic processes and may be a potential biomarker for EoE [105]; CD23 has been detected in stools of children with food allergies, but not in controls [49].

Cytokines and chemokines that mediate eosinophilic inflammatory processes include IL-5, which is crucial to eosinophil life cycle, and eotaxin-3, a eosinophil chemoattractant. IL-5 is intimately involved in eosinophil proliferation, maturation, trafficking, stimulation, degranulation, and recruitment [89]. Eotaxins are a family of chemokines that attract eosinophils and promote their degranulation and may also be involved in eosinophil homing to the gastrointestinal tract [58]. In a genome-wide microarray expression analysis, the gene-encoding eotaxin-3 (CCL26) was found to be the most highly induced gene in patients with EoE compared to normal individuals [8]. Eotaxin-3 levels in blood and esophageal tissue may also correlate with esophageal eosinophil density in pediatric patients [8, 47] though other studies have shown eotaxin-3 levels in esophageal tissue of EoE patients to be similar to controls with instead upregulation of TNF-α, eotaxin-1, IL-5, and IFN-γ in EoE subjects [34, 91]. Furthermore, eotaxin-1, eotaxin-2, and IL-5 in the peripheral blood have not been shown to correlate with esophageal eosinophilic inflammation [47]. More studies need to be performed looking at cytokines and their relation to EoE as information from studies to date have been conflicting [8, 34, 47, 91].

EDN is a toxic mediator released on degranulation of eosinophil cytoplasmic granules [36]. It is elevated in serum and urine of children with allergic atopic dermatitis and asthma [37, 47]. Plasma and stool EDN levels may correlate with eosinophilic esophageal inflammation and be useful as a noninvasive biomarker [10, 47, 75].

Radiological Studies An upper gastrointestinal (UGI) contrast study is useful to determine if there is any narrowing or any other gross anatomic changes associated with EoE. Narrowing of the esophagus, though uncommon in clinical practice, has been reported in up to 6 % of children with EoE [50]. Other findings include Schatzki's ring, corkscrew esophagus, and small-caliber esophagus [50]. The study may help map out the length and approximate positioning of strictures. Having information from an UGI study prior to endoscopy is helpful for planning the procedure – selection of endoscope size, caution for increased risk of mucosal tearing, and availability of dilation instruments. However, even in pediatric patients with documented food impaction, the UGI findings may be normal and not suggestive of luminal stricturing [7].

Esophagogastroduodenoscopy Signs of EoE seen on endoscopy include edema, loss of vascular pattern mucosal thickening, vertical lines, furrowing, white specks/plaques, and circular rings or trachelization of the esophagus. Up to 12 % of patients will have rings in their esophagus on initial endoscopy [50]. Strictures may require

dilatation, though the mucosa tends to be friable and associated with increased risk of deep mucosal tears and perforation. Abnormal endoscopic findings are not limited to the distal esophagus as may be the case with GERD but rather in the mid- and proximal esophagus too. Interestingly, patients with active EoE may have endoscopically normal-appearing mucosa; about one third of patients with normal endoscopic findings have severe eosinophilia on histology [50].

Histology Mucosal biopsies should be obtained from all patients with suspected EoE undergoing EGD. Obtaining biopsies from both the distal and mid-esophagus helps to differentiate the diagnosis from GER as changes in EoE are generally not limited to the distal segment [28]. Histological changes associated with EoE include intraepithelial eosinophilia, eosinophil microabscess, eosinophil degranulation, basal cell hyperplasia, vascular papillae elongation, mucosal edema, and lamina propria fibrosis [28]. The actual intraepithelial eosinophil cutoff number to differentiate EoE from GERD has been variable and of debate [18] – commonly >20 eosinophils/hpf has been employed; however, consensus recommendations are that ≥15 eosinophils/hpf should be used [28]. When correlating eosinophils with GERD, patients with < 5 eosinophils/hpf were more likely to have abnormal pH probe results than those with ≥20 eosinophils/hpf [80]. The number of eosinophils found in esophageal epithelial biopsies may vary depending on a number of confounding factors such as the size of hpf, number and site of biopsies, use of corticosteroids, sampling error, and seasonal variation [24, 69]. Eosinophilic microabscesses are clusters of 4 or more eosinophils and have been seen exclusively in patients with EoE [71, 102]. The eosinophilic infiltrate often is concentrated in the superficial epithelium [19, 102]. Special staining for eosinophils, Luna eosinophil granule stain, may be more sensitive in detecting eosinophils and can be useful in cases where the eosinophil count is indeterminate, i.e., 5–15 eosinophils/hpf [48]. A small study showed an increase in esophageal EDN on immunofluorescence staining in EoE patients by [44]. It is important in patients being evaluated for EoE to biopsy the stomach and duodenum in order to differentiate from other disease entities such as eosinophilic gastroenteritis.

pH Probe Extended intraesophageal pH monitoring may be performed to help differentiate EoE from GERD, though approximately 10 % of patients with EoE may have coexisting GERD [80, 90, 102]. Patients without evidence of pathological acid reflux on pH probe and persistent clinical symptoms as well as histological eosinophilia (≥20 eosinophils/hpf) are likely to have EoE [90, 102]. The degree of esophageal eosinophilia does not correlate with the degree of measured GER, and those with ≥20 eosinophils/hpf have an increased likelihood of a normal pH probe. Children with EoE may actually have increased alkaline reflux with pH values >8.0 occurring during 19 % of probe time vs. 0.9 % in age-matched controlled ($p<0.01$) [80]. Alkalization of the esophagus may be secondary to dysmotility causing delay of saliva passage or perhaps due to bicarbonate production from damaged submucosal glands [84, 99].

Endoscopic Ultrasound (EUS) Limited data is available for the utility of EUS in the diagnosis of EoE although thickening of the mucosa, submucosa, and muscularis propria is seen compared to children without EoE [26]. In this single study, 11 patients were diagnosed with EoE based on four criteria: (1) endoscopic and histological appearance consistent with EoE, (2) extended esophageal pH probe results, (3) nonresponse to twice-daily proton pump inhibitor (PPI) therapy, and (4) symptomatic and histopathological response to swallowed fluticasone. EUS measurements were obtained 3–5 cm from the gastroesophageal junction, and layers measured were (1) total wall, (2) mucosa + submucosa, (3) muscularis propria, and (4) circular muscle. All layers except the circular muscle were statistically thicker in the EoE patients compared to controls.
Esophageal Manometry – Patients with EoE may experience dysphagia, without evidence of strictures or other anatomic abnormalities, suggesting esophageal dysmotility though it is unclear

whether esophageal manometry is useful for evaluation and/or management of EoE. One study using prolonged (24-h) esophageal manometry measured an increase in ineffective peristalsis and isolated and high amplitude contractions in pediatric patients with EoE compared to patients with GERD and controls [68]. It should be noted that traditional esophageal manometry may not show any motility abnormalities in the pediatric population [12]. Adult manometry studies have been inconclusive, but 10–57 % of patients may have nonspecific esophageal motor disorders [6, 16, 53, 55].

Treatment

The end point of EoE treatment is unclear, the long-term impact of the disease is still unknown, and there is dissociation between symptoms and objective data. Should the end point be based on symptoms, endoscopic findings, histological abnormalities, or a combination of these or some other criteria? A patient who is asymptomatic/has nonspecific symptoms may have endoscopic findings consistent with EoE. Another patient with normal/unremarkable endoscopic appearance may have severe eosinophilic infiltration on histology. Various treatment options for EoE are available and include dietary modification, systemic and topical steroids, biologic agents, and esophageal dilation.

Dietary Modification A broad-brush elemental diet, consisting of amino acid (AA)-based formula only, can be very successful in the motivated patient and family (88–97.6 % response [40, 43, 50, 56]). In the original article by Kelly et al. [43], ten children were placed on an elemental diet for a minimum of 6 weeks, of which eight showed clinical resolution and two had improvement. The number of esophageal epithelial eosinophils decreased from a median of 44 eosinophils/hpf pretreatment to 0.5/hpf on treatment. In a review of 60 pediatric patients with EoE (35 patients on a six-food elimination diet, 25 on an exclusive AA-based formula diet), 74 % of the patients on the six-food elimination diet and 88 % of the patients on the AA-based formula diet showed a reduction in eosinophils to ≤10/hpf [40]. Expected clinical improvement occurs within 1–2 weeks of strict adherence to an elemental diet; in 51 EoE patients on an elemental diet, 8.5 ± 3.8 days was the time to clinical improvement with endoscopic and histological improvement by 1 month [56]. Foods can be reintroduced slowly after confirmation of histological improvement, though the reintroduction may result in disease recurrence which then necessitates repeated endoscopies.

More liberal diets guided by results of allergy testing are termed directed-elimination diets. In treatment of 146 children with EoE, skin prick test (SPT) and atopy patch testing (APT) were performed to guide elimination diet [85]. In this report, 75 % of patients responded in 6–8 weeks to elimination of positively tested foods with clinical and histological improvement. Many patients however relapsed with reintroduction of allergic foods [85]. Interestingly younger children are more likely to respond to dietary elimination. The likelihood of identifying a food allergy depends on the number of foods tested, and most commonly identified food allergies on SPT are milk, eggs, soy, wheat, fish, and peanuts, and APT most commonly identified positive reactions to milk, wheat, corn, beef, egg, potato, chicken, soy, barley, oat, and rice in patients with EoE (Table 61.3) [86]. SPT is aimed at identification of IgE-mediated allergies, whereas APT identifies T-cell-mediated, non-IgE-mediated allergens. Since EoE is likely due to a combination of both IgE- and non-IgE-mediated allergy, performing both SPT and APT may increase the likelihood of identifying

Table 61.3 Six most commonly allergenic foods seen with EoE

Dairy
Eggs
Wheat
Soy
Peanuts
Fish/shellfish

Table 61.4 Riley hospital diet for EoE

Food or beverage	Avoid	Allowed
Beverage	Milk, soy milk, juice drinks, all fruit juice except pure juice from 5 selected fruits, tea, coffee, all formulas other than Neocate, Neocate One+, Neocate Jr., pediatric EO28, or Elecare	Water, Neocate, Neocate One+, Neocate Jr., pediatric EO28, or Elecare, rice milk, pure fruit juice from 5 selected fruits[a]
Animal protein sources	Cheese, eggs, poultry, fish, all meats except lamb	Lamb
Vegetable protein sources	Soy milk, soybeans, all beans, lentils, peas, peanuts, peanut butter, all nuts, bean sprouts	None
Grains/starches	Wheat, corn, oats, barley, rye, millet, wild rice	White potato, buckwheat, sweet potato, yams, rice, tapioca, arrowroot
Vegetables	Peas, tomatoes, corn, green beans, lima beans, cucumber, summer squash	Limit to 5 choices from the allowed vegetable list
Fruits	Citrus fruit (orange, tangerine, grapefruit, lemon, lime), all berries, cherries, kiwi, canned fruits in syrup	Limit to 5 fruits from the allowed fruit list[a]. Fruits may be fresh, frozen, juice, or canned in water or juice
Sweeteners	Powdered sugar	Cane or beet granulated sugar, maple syrup, honey, corn syrup, molasses, brown sugar
Fats/oils	Butter, all margarines except milk-free, nonspecific shortening, fats of animal origin	Coconut oil, corn oil, safflower oil, soy oil, milk-free margarine[b]
Other	Chocolate, malt, cornstarch, baking power	Salt, pepper, spices (limit total number to 5), vanilla extract, lemon extract baking soda, cream of tartar. Yeast, distilled vinegar, soy, lecithin[b]

[a]See Table 61.5
[b]No corn is allowed except corn oil, no soy is allowed except soy oil and soy lecithin, and oils must be hot pressed

Table 61.5 Riley hospital diet for EoE

Allowed vegetables	Allowed fruits
Asparagus	Apple
Beets	Apricot
Broccoli	Banana
Brussel sprouts	Cantaloupe
Cabbage	Grapes (seedless)
Cauliflower	Mango
Celery	Peach
Green pepper	Pear
Lettuce	Pineapple
Onion	Plum
Spinach	Raisins (seedless)
Turnips	
Winter squash	

offending foods. Using SPT alone may be insufficient in identifying all potential allergens, leading to treatment failure [66, 98]. Empiric food elimination of the six most commonly allergenic foods, namely, milk, eggs, soy, wheat, fish, and peanuts, has been successful in 74 % of children with both clinical and histological improvement [40]. While patients may test positive for food allergies on radioallergosorbent testing (RAST), no studies have shown successful treatment using RAST as a guide for food elimination [70, 98]. The elimination diet we offer our patients, in addition to directed-elimination and elemental diets, is listed in Tables 61.4 and 61.5. Many EoE patients have coexisting allergic rhinitis and aeroallergies [3, 62, 69] which should be appropriately managed and treated.

Systemic Corticosteroids Oral prednisone induces both clinical and histological remission in >95 % of pediatric EoE patients [50] though there is a risk of disease relapse (as with dietary modification) after weaning of

treatment. Dosing for prednisone is 1–2 mg/kg/day, divided twice a day, with a maximum of 60 mg/day [50, 81]. The risks associated with using systemic corticosteroids for EoE are the same as with any other indication (Table 61.6). There is no identified optimal weaning strategy to decrease incidence of relapse, though a slow taper is indicated for patients who have been on prolonged treatment due to risk of adrenal insufficiency and to perhaps delay likelihood of symptom relapse. In a study of 80 pediatric EoE patients randomized to oral vs. topical corticosteroids, there were no significant differences in the rate and progression to disease relapse among the two therapies [81].

Topical Corticosteroids Corticosteroids are delivered into the esophagus topically by swallowing formulations typically used as inhaled treatment for asthma. The major benefit of using topical therapy is the avoidance of side effects caused by systemic corticosteroids. Fifty two to 100% of patients treated with swallowed fluticasone had improvement of their symptoms [50, 98]; significant histopathological improvement is also induced by topical corticosteroid treatment. Treatment dosing of swallowed fluticasone from a metered dose inhaler (MDI) has ranged from 220 to 440 μg two to four times daily for a duration of 6–12 weeks. No standard treatment protocol has been developed to date, but dosing listed in Table 61.7 can be used as a prototype. Patients are to place the inhaler directly in their mouth with a tight seal, administer two puffs, swallow, and abstain from rinsing or oral intake for 30 min. After 30 min, patients should take a drink of liquid to "wash down" the medication due to the risk of candidal overgrowth. Unlike treatment for asthma, a spacer should not be used. Oral viscous budesonide mixed with sucralose has also been used successfully in treatment of EoE with 80% of patients responding in one study [1]. Budesonide may be an option for children who are unable to coordinate use of a MDI.

Histopathological reassessment should be performed after 4–12 weeks of therapy, specifically after 4 weeks with fluticasone treatment and 12 weeks with budesonide therapy to demonstrate efficacy. As with systemic steroids, there is no standard weaning schedule, but patients may be weaned slowly over approximately 3 months with close clinical monitoring for disease relapse. The major side effect seen in patients using topical steroid therapy is candidal overgrowth of the esophagus [98]. There is the possibility of adrenal suppression, growth impairment, and other end-organ damages such as osteoporosis with chronic topical corticosteroid exposure though objective data is wanting.

Table 61.6 Side effects of systemic prednisone

Central nervous system	Headache, mood disturbances, psychosis, pseudotumor cerebri, intracranial hypertension
Ocular	Increased intraocular pressure, cataracts, glaucoma
Cardiovascular	Hypertension, edema
Gastrointestinal	Nausea, vomiting, peptic ulcer disease
Endocrine	Cushing syndrome, electrolyte disturbances, hyperglycemia, growth suppression, weight gain, hypothalamic-pituitary-axis suppression, menstrual irregularities
Musculoskeletal	Osteoporosis, fractures, muscle weakness
Immune system	Immunosupression
Dermatologic	Acne, impaired wound healing, skin atrophy, bruising, petechiae

Table 61.7 Topical steroid therapy dosing prototype for pediatric EoE

Medication		
Fluticasone propionate	Age 1–10 years – 110 μg, 2 puffs swallowed, 4 times daily	Age ≥11 years – 220 μg, 2 puffs swallowed, 4 times daily
Budesonide mixed with 5 g sucralose	Age 1–9 years – 1 mg daily	Age ≥10 years – 2 mg daily

Leukotriene Receptor Antagonists There have been no studies to date using leukotriene receptor antagonists in children for the treatment of EoE. No difference in cysteinyl leukotriene levels in esophageal mucosal biopsies was found between pediatric patients with and without EoE [35]. Eight adult patients with EoE and symptoms of dysphagia were treated with 20–40 mg of montelukast for a median of 14 months; six had symptomatic resolution but histopathological remission was not investigated, and all had symptoms relapse within 3 weeks of discontinuing treatment [5].

Cromolyn Sodium No formal studies have been published using cromolyn sodium in children with EoE. Fourteen pediatric patients who had been trialed on oral cromolyn (100 mg/dose four times a day) did not have clinicopathological improvement after 4 weeks of treatment [50].

IL-5 IL-5 is the primary cytokine responsible for eosinophil proliferation, maturation, and recruitment among other eosinophil-directed functions [4, 89]. A fully humanized anti-IL-5 antibody, mepolizumab, has been used with success in treatment of HES with significant sparing of systemic steroid usage [29, 57, 78]. An open-label phase I/II study conducted on four adult patients with EoE showed decrease in peripheral and esophageal eosinophilia with 750 mg mepolizumab infusions administered once a month for 3 months [88]. Peripheral eosinophilia, esophageal eosinophilia, and patient quality of life were compared prior to initiation of mepolizumab and 1 month after treatment. There was a decrease in peripheral eosinophilia by 6.4-fold and esophageal eosinophilia by 8.9-fold with therapy as well as improvement in patient symptoms scores and quality of life using the Validated Short Form Health Questionnaire SF-36. Adverse events noted with mepolizumab were headache and upper respiratory tract infections with one patient experiencing hypotension during the third infusion, which was successfully treated with volume expansion. In a double-blind, randomized trial, 11 adults with EoE were treated with mepolizumab or placebo – while a significant decrease in the number of eosinophils/hpf was reported, none of the biopsies fell below 15 eosinophils/hpf and clinical remission was not attained at the end of the trial [93]. Patients in this study were treated with mepolizumab 750 mg infusion or placebo 1 week apart for two infusions. Four weeks after the initial infusion, a repeat EGD was performed – none of the patients attained a eosinophil count of <15/hpf. Patients were then given mepolizumab 1,500 mg or placebo for two additional doses 4 weeks apart and EGD re-performed 4 weeks after the last infusion. Again no patient had an esophageal eosinophil count of <15/hpf, and side effects were minimal and included upper respiratory tract infection and fatigue.

While there is potential for anti-IL-5 to be used as targeted therapy in EoE, further study is needed and clinical trials are currently being conducted. An open-label study of three doses of mepolizumab in children with EoE having prior inadequate response or intolerance to other EoE therapies was recently completed [32]. Pediatric patients had a pharmokinetic profile similar to that of adults and 31 % of subjects achieved <20 eosinophils/hpf on esophageal mucosal biopsies. Another anti-IL-5 agent reslizumab is currently being evaluated in children with EoE.

Omalizumab This is a recombinant monoclonal IgG1 antibody, which binds IgE, and it has been used for the treatment of asthma and allergic rhinitis [9]. Nine adult patients with eosinophilic gastroenteritis were trialed on omalizumab with decrease in gastric and duodenal eosinophils, but the numbers did not reach statistical significance [25]. Of these nine patients, seven also had eosinophilic infiltration of the esophagus with >25 eosinophils/hpf. The study did not show decrease in esophageal eosinophils, and instead there was a statistically insignificant trend toward increasing number. No published trails exist for use of omalizumab specifically for EoE.

Acid Suppression The use of acid-suppressive agents including PPI in EoE is a matter of much debated. In one retrospective study, 43 pediatric patients with esophageal eosinophilia of ≥15/hpf were treated with a PPI [21]. On repeat endoscopy,

17/43 (40%) of the patients had ≤5 eosinophils/hpf, while 86% reported symptomatic response. Abnormal pH probe, reported symptoms, endoscopic appearance, baseline eosinophil count, and season of presentation did not have statistically significant correlation to PPI response, and hence it is difficult to clinically predict who will demonstrate histological response to acid-suppressive therapy. Acid suppression may be of benefit if the patient has overlapping EoE and GERD since up to 10% of patients with EE have this coexisting GERD [80, 90, 102]. In a case series of three patients with esophageal eosinophilia of ≥20/hfp, treatment on PPI alone induced histological remission in all patients (eosinophils of 0–3/hpf) after 4–8 weeks [65]. Although the patients in this case series met histological criteria for diagnosis of EoE, it is important to note that reflux esophagitis may well cause significant eosinophilic infiltration as one patient did have an abnormal reflux index on pH probe and the other two did not have a pH probe performed. PPI treatment may also be useful in diagnosis of EoE since nonresponse along with eosinophilic infiltration of the esophagus is virtually diagnostic of EoE in the appropriate clinical situation.

Infliximab Infliximab is a chimeric TNF-α inhibitor used in the management of chronic inflammatory conditions such as rheumatic arthritis and inflammatory bowel disease. A single study involving three adult patients with corticosteroid-dependant EoE used infliximab as a therapeutic option [92]. All other EoE treatments were discontinued for a 4-week period followed by infusion of infliximab 5 mg/kg for two doses spaced 2 weeks apart. There were no statistically significant results with regard to symptoms score, number of eosinophils/hpf, esophageal inflammatory mediators, TNF-α levels, or eotaxin-3 levels.

Esophageal Dilatation Non-pharmacologic intervention for EoE may be needed in patients who have strictures unresponsive to medical management, but data on the use of esophageal dilation in the pediatric population is limited. In a retrospective review of a single center over a 5-year period, balloon dilation was performed in 31% of their pediatric EoE patients [77] with symptomatic improvement in the patients and no reported major complications. Although esophageal perforation is rarely reported, care must be taken while performing the procedure as there is increased risk for deep mucosal tearing and significant postoperative pain [41, 63, 82, 101]. Most adult series have used bougienage dilatation, and 7–50% required repeated dilation for stricture recurrence [63, 94, 96]. Deep mucosal tears and renting can occur with introduction of the endoscope alone, and therefore care must be taken to select an appropriately sized endoscope if narrowing is suspected. There is no data available to determine if pretreating dilation medically will improve outcomes or decrease risk of trauma, though we do prefer this approach in our clinical practice. Given the risks of complications, surgical management should be reserved for those failing medical therapy or for those with a critical stricture.

Long-Term Outcomes

It is difficult to maintain histological remission after discontinuation of dietary or medical therapy, and it appears that EoE is a chronic disease and prone to relapse off-therapy. In a population of 562 patients with EoE, only 11 (1.9%) were able to maintain remission off-treatment [24]. Untreated disease can be complicated by esophageal narrowing and stricture, and younger children may have persistent feeding intolerance or failure to thrive. Patients may remain asymptomatic despite recurrence of esophageal eosinophilia though in-depth questioning including for coping mechanisms should be performed. There currently is no evidence for increased incidence of metaplasia, adenocarcinoma, or progression to any other gastrointestinal diseases in patients with EoE, though more longitudinal data is needed.

Conclusions

Eosinophilic esophagitis is a complex and currently incompletely understood entity though rapid and significant advances in our

understanding of this disease have been made over the last decade and half. The pathogenesis is an interplay of genetic predisposition with environmental and dietary contributions, but the pathways and triggers to disease expression have yet to be elucidated. Diagnosis is complicated by nonspecific symptomatology as well as comorbid conditions such as gastroesophageal reflux. Selecting the type and duration of treatment can be a dilemma for the clinician as response, treatment dependence, and risks for disease relapse are unpredictable and inconsistent. Treatment tolerability is also an issue since systemic corticosteroids have significant side effects and strict dietary modifications are difficult to adhere to chronically. Inhaled corticosteroids are better tolerated but not scientifically studied in EoE therapy, and novel therapeutic agents are being investigated. EoE is a chronic disease with potential for esophageal fibrosis, and restructuring and longitudinal studies are needed to better define these complications and disease natural history. Many aspects of EoE remain unknown to date, but much research is ongoing and the results will surely prove fascinating and enlightening.

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Eosinophilic Esophagitis (Europe)

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Introduction and Definition

Eosinophilic esophagitis (EE) is an emergent disease suffered by patients of any age, often bearing allergic symptoms, who experience abdominal pain, vomiting, heartburn, dysphagia or food impaction associated with heavy eosinophilic infiltration, edema, and inflammation of the esophageal mucosa. The fact that some of its symptoms and the main histologic features are also observed in gastroesophageal reflux disease (GERD) makes diagnosis between both conditions confusing. However, the normalcy of pH studies and the lack of response to acid suppression in many EE patients together with the favorable effects of anti-inflammatory medication and dietary restrictions and elemental diets in them [36] allowed its recognition as an individual disease with its own clinical, endoscopic, and histologic features. EE is increasingly prevalent both in children and adults and indeed deserves separate study.

History

EE was first described as an independent disease by Atwood et al. in 1993 [5], and the number of publications on this topic increased over the last two decades in parallel with its amazingly growing prevalence. It should be pointed out that, at the same time, other eosinophilic gastrointestinal ailments became accordingly frequent, revealing a common background. The intensity of the eosinophilic infiltration required for diagnosis has been a matter of debate [21] until cutoff values of eosinophils were set for diagnosis [47] in order to separate true EE from reflux esophagitis with eosinophilic infiltration. These cutoff values are relevant because until then, it had been accepted that one of the histologic criteria for the diagnosis of reflux esophagitis was eosinophilic infiltration of the mucosa [33]. Experienced pathologists soon concurred in that the intensity of this infiltration in EE was well beyond what it was seen in GERD. EE occurrence in children was pointed out simultaneously with its description in adults, and, although there are differences in clinical expression, analysis and recommendations for

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diagnosis and treatment have been shared by adult and pediatric gastroenterologic associations [25].

Etiology and Pathogenesis

The origin of EE remains unknown, although an allergic mechanism is more than likely. All ethnic groups are affected, but the disease is more prevalent in white individuals, and it is definitely more frequent in males (3:1 in children) [25] with some familial predisposition [13, 49, 64]. Differences in reporting could account for the apparent regional discrepancies in prevalence, but there is no doubt that blind retrospective studies in developed countries demonstrated a substantial increase over time [17, 57].

The amazing concentration of eosinophils in the esophageal mucosa was found to be related to increased levels of the chemoattractant eotaxin 3 [11], and it was shown later that EE patients had a unique genetic profile with highly induced eotaxin 3 (or CCL26) gene. In addition, knockout mice for this gene were immune to experimental EE [12], and increased eotaxin 3 messenger could be demonstrated by RT-PCR in esophageal biopsies of individuals with EE in contrast with both controls and GERD patients [7]. The Th-2 cytokine interleukin IL-5 seems to participate also in this eosinophil chemoattraction together with eotaxin 3 since IL-5 overexpressing transgenic mice under the control of a T cell (CD2) have increased eosinophils in the esophagus that decrease in the absence of eotaxin 3 [51]. Other interleukins like IL-3 and IL-13 play also a role in EE [8, 10], and increased T cell and mast cell numbers were found within the epithelium of EE patients together with increased expression of IL-5 and TNF-alpha [81]. The obvious interpretation is that EE is of allergic nature, and there is ample evidence of the participation of alimentary allergens in human EE since restriction and/or elemental diets improved the disease [36]. On the other hand, aeroallergens may also unchain these allergic reactions. Mice challenged with respiratory allergens (but not with gastrointestinal ones) developed marked esophageal eosinophilic infiltration [50]. It has also been shown that sensitization to both food and aeroallergens participate in the pathogenesis of EE in children [66].

Recently, an association between celiac disease (CD) and EE [62, 90] was confirmed [42]. The prevalence of EE in esophageal biopsies of CD patients was 4% or higher, and infiltration persisted in some children after duodenal histologic recovery under gluten-free diet [42]. This association is intriguing because EE is a Th-2-mediated disorder, whereas CD is a Th-1-mediated condition. The increased permeability of the intestinal mucosa in CD could allow exposure of the immune system to various antigens and generate distant hypersensitivity responses like EE [42].

The allergic nature of EE was unveiled when dietary management with either elemental diets [36] and/or elimination of six foods (cow-milk protein, soy, wheat, egg, peanut, and seafood) cured the symptoms and the eosinophilic infiltration in children [34]. At the end of dietary treatment, infiltration reappeared in some cases [36]. Allergic symptoms like atopic dermatitis, eczema [43], rhinitis and/or sinusitis, laryngitis, or bronchial spasm-asthma are frequent in children with EE [30, 63, 89].

The inflammatory reaction of the esophageal wall impairs in some way the propulsive function of the organ. Edema and narrowing, the cytokines themselves, changes in intrinsic innervation or secondary muscular disorders explain defective peristalsis and symptoms like dysphagia or food impaction [58, 59].

Pathology

Basal layer thickening [52, 79] and papillar lengthening [65] are present in EE. These features, together with infiltration of the mucosa by eosinophils [31, 41], had been considered indicative of reflux esophagitis in children. However, in recent years, heavy infiltration in excess of 20 eosinophils per high power field (hpf) (or better $\geq$15 per hpf) in at least one mucosal biopsy was set as a diagnostic threshold for the diagnosis of EE [25]. Apparently, peak count of eosinophils in the most involved hpf correlates with highest

average count per hpf count. This, together with the use of specific Luna eosinophil granule stain, could simplify diagnosis [40]. The absence of eosinophilic infiltration of the mucosa of other parts of the GI tract has been included into the diagnostic criteria for EE [15].

Thickening of the mucosa, friability, and even narrowing of the lumen observed upon endoscopic assessment attest the transmural involvement of the esophagus in the disease. These features may correspond to subepithelial fibrosis [52] which was present in children with EE but absent in those with either eosinophilic gastroenteritis or GERD [16]. The increased collagen in the lamina propria was only visible with Masson trichrome stain in relatively deep biopsies and was constant in children with food impaction. It was not associated with increasing numbers of either eosinophils or mast cells in the mucosa, but it was associated with activation of eosinophils as shown by degranulation [16]. Ulcers are not seen in EE, but abundant desquamation and exudates may be present.

Clinical Features in Children

The main symptoms of EE in infants and young children are refusal to feed, vomiting and abdominal pain, or dysphagia expressed as discomfort. Later on life, when the patient becomes able to describe his symptoms, abdominal or epigastric pain, vomiting or regurgitation, heartburn, dysphagia, or food impaction become the leading features [18, 20, 28, 43, 63, 68, 88]. Patients have to swallow water to pass solid food, and eventually the bolus impacts itself into the esophageal lumen and blocks any attempt at swallowing. This brings sometimes the patient to the emergency room and triggers the diagnostic work-up [46]. Failure to thrive or diarrhea may be experienced sometimes by children with EE. With these symptoms, except when food impaction or obvious allergic disease occurs, the first diagnostic suspicion and hence the first treatment measures are directed to treat GERD. Only after endoscopic assessment will failure of pH probe to demonstrate GERD or persistence of the symptoms in spite of energetic acid suppression the possibility of EE be considered. Schatzki rings [60] and spontaneous rupture of the esophagus (Boerhaave syndrome) [82] have been occasionally observed in this condition.

Most children with EE, up to 60–80 %, have allergic symptoms like rhinitis, laryngitis, asthma, or eczema, indicating the atopic nature of the disease [43]. This should raise the level of suspicion and prompt diagnostic work-up. Blood eosinophilia may also be present in EE [68], and to a certain extent, it correlates with the intensity of esophageal eosinophil infiltration [73].

It was recently pointed out that EE or intermediate esophagitis (IE), a minor form in which the intensity of infiltration does not reach diagnostic levels, may occur in patients operated upon for esophageal atresia and tracheoesophageal fistula [61]. In these individuals, GERD is extremely frequent, and, since they have often dysphagia due to the original condition and its surgical repair, the diagnosis of EE may be missed and the appropriate treatment never undertaken.

Diagnosis

Except in cases with obvious atopic symptoms and perhaps when food impaction occurs, the diagnosis of EE is only made after excluding other possible conditions and particularly GERD. This implies that pH monitoring and fiber-optic endoscopy with biopsy are necessary, often after more or less prolonged attempts at acid suppression with high-dose proton pump inhibitors (ppi). In a number of EE patients, true GERD occurs at the same time, and this creates some confusion.

Barium meal may show narrow esophageal lumen, dysmotility, or Schatzki rings [60]. Computed tomography has shown thickened esophageal walls in a few children with EE [68] and so did esophageal ultrasonography which demonstrated thickened mucosal, lamina propria, and submucosal layers [24].

Ambulatory pH metering may reveal excessive acid exposure in children with EE; although since it is used to exclude GERD in these cases,

this feature can be attributed to it. Excessive alkaline exposure has been observed in some patients [68].

Stationary and prolonged ambulatory esophageal manometry in children revealed that peristalsis is abnormal in terms of either poor or excessive amplitude of the waves, frequent tertiary waves, and abnormally propagated waves. Some of the abnormal motor events were accompanied by dysphagia [59], and they were particularly marked in the distal esophagus and during nighttime [46]. This pattern of dysmotility is quite similar to that described in adults, in whom, in addition, lower esophageal sphincter pressure has been found to be normal or slightly decreased [6, 44]. Combined pH and multichannel prolonged impedance studies in children with GERD and EE showed that, as expected, there was increased acid exposure in GERD that the mean number of nonacid refluxes was similar in both conditions and that no full-column reflux episodes were more frequent in EE than in GERD [67].

Endoscopy may show an apparently normal mucosa in one third of children and edema, friability, longitudinal furrows, and white plaques and exudates in the remaining two thirds [43]. In some patients, concentric rings give to the esophagus a "trachealized" [2] or "feline" aspect [35, 48] for it resembles what is common in the cat esophagus. True stenosis may occur in a few cases [19, 36], but in most, the instrument can be advanced along the esophagus although with frequent fissuration of the mucosa [53].

Biopsies should be taken at various levels and, ideally, also from other segments of the GI tract for involvement of the mucosa outside the esophagus is more likely due to eosinophilic gastroenteritis. The number of eosinophils per hpf authorizes diagnosis when the solid cutoff of $\geq$15 per hpf is attained in at least one of the specimens with an understandable increase in sensitivity when several biopsies show the infiltration [29]. Detailed observation of the sections can demonstrate the presence of groups of eosinophils and in some cases of micro-abscesses [86] made up of these cells.

Some diagnostic tests directed to unveil the allergic nature of EE are usually included in the work-up: blood eosinophilia, which is found in half of the affected children or more [68] and correlates to a certain extent with mucosal eosinophil count [38]; total IgE, which is usually elevated and falls after corticosteroid treatment; and aeroallergen and food-specific IgE radioallergosorbent testing (RAST) [91] which yield variable results. Plasma cytokines, like IL-5, IL-13, or the chemoattractant eotaxin-3, are elevated in EE [38] and usually decrease after treatment. Finally, skin prick testing [75, 76] and patch tests for atopy [76, 77, 85] may unveil sensitization to various allergens and guide food elimination treatment.

Natural History

EE is a chronic disease that may persist for years. A follow-up study of 30 adults showed that, after more than 7 years, majority still experienced dysphagia although without nutritional impact or apparently malignant potential [84]. Although this is reassuring, the chronic inflammation could have some unknown permanent impact on esophageal function [80]. The fact that EE is not a mucosal destructive condition like GERD explains why Barrett's esophagus and/or adenocarcinoma are not observed in this condition [25]. It has been questioned whether natural history would be the same in children and adults with EE [87]. Elimination and elemental diets, corticosteroids, and Montelukast are usually effective for alleviating symptoms and also for decreasing mucosal infiltration, but most studies do not include sequential biopsies able to rule out the persistence of the disease in the long run. An 8-year follow-up study of 89 children with EE showed that the vast majority of those responding to treatment relapsed [3]. In another study involving 330 children with EE followed up for more than 1 year, no progress to any other gastrointestinal disease was detected [78]. Personal or family anxiety is also a cause of concern in these chronically ill children [37].

Treatment

Due to the elusive nature of EE, it is difficult to assess the results of treatment that can aim at relieving the symptoms, reverting the mucosal

infiltration, or both. The clinical and pathologic features shared by EE and GERD tend to dilute the therapeutic aim: if persistence of symptoms after formal PPI treatment is required for the diagnosis of EE, it will be the disappearance of these symptoms, but if, on the contrary, the diagnosis is made upon finding of dense eosinophilic infiltration of the mucosa, it may be obviously different. Finally, if the leading symptoms are allergic, the aim may be the clearance of any cutaneous, respiratory, or biologic sign of the disease together with the symptoms.

The following treatment measures have been used in children with EE:

1. Acid suppression: The diagnosis of EE is done in most cases after ruling out GERD. The latter is often treated by acid suppression drugs prior to the performance of invasive tests, and therefore, a full course of PPI has usually been completed in all patients [70]. Persistence of the symptoms prompts the performance of diagnostic tests and allows the correct diagnosis. It is probably wise to treat all patients with PPI for some time.
2. Dietary food suppression has been very successful after skin prick and/or patch testing for food allergens and even without these tests [34, 69, 76]. Elimination of six usually taken foods (cow-milk, soy, wheat, egg, peanut, and seafood) improved EE in children [34] and is a good diagnostic and therapeutic test.
3. Elemental diets can be used when there is evidence of wide sensitization or when food elimination fails. This dietary management, which is highly effective and able to revert the esophageal eosinophilic infiltration [47], is less practical due to the limited acceptability by patients for prolonged periods of time, but it has been useful in numerous cases.
4. Systemic corticosteroids are dramatically effective as expected in an allergic condition like EE. However, the necessary doses (1–2 mg/kg/day of prednisone) prescribed for relatively long periods of time involve undesirable secondary effects that are prevented by topical treatment [71]. In addition, a rebound effect is possible after cessation of long-term treatment. In consequence, this medication should only be used in severe acute cases of after failure of nutritional or topical treatments [55].
5. Topical corticosteroids, administered in the form of aerosols (fluticasone propionate, 200–400 μg twice a day), were highly effective for alleviating the symptoms, decreasing esophageal infiltration by eosinophils and CD3 and CD8 lymphocytes [56, 88]. A randomized blind trial showed that fluticasone was significantly better than placebo in terms of disappearance of symptoms and decrease of infiltration on the mucosa by eosinophils and T(+) lymphocytes [39]. Candida overgrowth has been pointed out in a reduced proportion of patients after this treatment [71]. Budesonide in a viscous suspension produced good results in children with EE [1].
6. Leukotriene inhibitors like Montelukast at 20–40 mg/day during prolonged periods of time were successful in most cases, although relapses were seen after cessation of medication [4].
7. Other medications, like inhibitors of [32] or monoclonal antibodies [14, 26, 74] against IL-5, or immunomodulators [54] have been also used occasionally. There is experimental evidence of some effect of pretreatment with monoclonal antibodies against IL-13 of the esophageal effects of this cytokine [9].
8. Esophageal dilatation: In cases in which severe dysphagia is due to stenosis, formal dilatation is indicated [72]. However, the mucosa is particularly fragile in EE [83], and there are risks of tearing and even of perforation in adults [22, 45] and children [27]. If possible, endoscopy and dilatation should be deferred until after medical treatment has been instituted.
9. Impacted food bolus extraction may be necessary and is one of the operations leading to the diagnosis of EE in children [23, 68]. In all cases in which food impaction in the absence of stenosis occurs [46], esophageal biopsies and blood samples for peripheral eosinophilia and biologic markers should be taken in order to make diagnosis possible.

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Effect of Systemic Illness, Medication, Radiation, and Infection on the Esophagus

63

Seema Mehta and Ryan W. Himes

Introduction

Injury to the esophagus can result from infection, medical therapy, or systemic illness. *Candida*, herpes simplex virus, and cytomegalovirus comprise the bulk of clinically encountered esophageal infections. Esophageal injury secondary to medical therapy is most often caused by retained pills; however, chemotherapy and radiation therapy are also associated with esophagitis. Systemic diseases involving the connective tissue, skin, and neuromuscular system may also affect the esophagus, usually giving rise to dysmotility or mucosal injury. Although these etiologies of esophageal injury occur less frequently in the pediatric population, physicians and surgeons charged with the care of children should nonetheless be aware that esophageal symptoms may be the presenting feature of one of these systemic conditions.

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Infectious Esophagitis

Three organisms account for most cases of infectious esophagitis, *Candida* spp., herpes simplex virus (HSV), and cytomegalovirus (CMV), and are discussed in detail below. Primary bacterial infections of the esophagus are uncommon [146]. There is considerable symptomatic overlap in infectious esophagitis of any etiology, underscoring the value of upper endoscopy as the gold standard in their diagnosis.

Candida

Epidemiology and Pathophysiology

Candida albicans is a normal commensal in the gastrointestinal tract. Because of its ubiquity *C. albicans* is the most commonly encountered esophageal pathogen [140]. While most cases of *Candida* esophagitis occur among the immunocompromised, widespread availability of highly active antiretroviral therapy has heralded a declining prevalence of this once extraordinarily common complication in the human immunodeficiency virus (HIV) population [101]. *Candida* esophagitis may also be the initial manifestation of autoimmune polyendocrinopathy-candidiasis-ectodermal

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dystrophy (APECED) syndrome (OMIM 607358) in children.

The pathophysiology of *Candida* esophagitis is a two-step process, colonization of the esophagus followed by invasion and more rarely dissemination [9]. Factors favoring this process include esophageal stasis, lack of competitive inhibition from microbial communities, and defective lymphocyte and granulocyte function. In addition to primary immunodeficiency states, risk factors for *Candida* esophagitis are corticosteroid use (both inhaled [54, 95, 137] and systemic [24, 95]), antibiotic therapy [24], presence of underlying esophageal injury (e.g., caustic ingestion) or motility disorder, gastric hypochlorhydria (e.g., proton pump inhibitors) [24, 65, 95, 137], as well as chemotherapeutics and immunosuppressants in the context of bone marrow or solid-organ transplantation.

Clinical Manifestations

In a series of immunocompromised pediatric patients with esophageal candidiasis, odynophagia was present in 80 %, retrosternal pain in 57 %, and dysphagia in 45 %; nearly all episodes (94 %) presented with concomitant oropharyngeal candidiasis [23]. Rare complications of advanced disease that have been described include esophageal stricture and perforation as well as systemic dissemination. In infants the main symptom may be a refusal to eat.

Diagnosis

Endoscopically, esophageal candidiasis usually presents with white plaques that will not wash away upon irrigation on an erythematous and friable background. Edema, cobblestoning, and linear confluence of the plaques, which are comprised of fungal elements and sloughed cellular debris, are common. Discrete ulcers, on the other hand, should raise the question of a coexistent, usually viral, infection.

Mucosal biopsies should be obtained for cytological examination. Yeast, hyphae, and pseudohyphae are readily demonstrated with routine stains. Culture is not useful unless susceptibility testing is desired (i.e., when a resistant organism is suspected).

Under the right circumstances (e.g., immunosuppressed child with odynophagia, chest pain, and oropharyngeal candidiasis), some clinicians would empirically treat for *Candida* esophagitis and reserve endoscopy for those who did not respond to an appropriate agent.

Treatment

Mild cases in hosts with a reversible or transient risk factor such as swallowed corticosteroids for eosinophilic esophagitis or antibiotic use may respond to cessation of that agent. Oral fluconazole has the advantage of once-daily dosing and is the mainstay of treatment in patients capable of swallowing medications [1]. Treatment is continued for 2–3 weeks after symptomatic improvement [1]. Amphotericin B should be used parenterally for patients with neutropenia and fever or disseminated disease [146]. Caspofungin is an alternative; it was shown to be as efficacious as amphotericin B in a randomized trial among predominantly HIV-positive adults with *Candida* esophagitis [138].

The Infectious Disease Society of America recommends fluconazole for prevention of fungal disease in neutropenic patients undergoing chemotherapy or bone marrow transplantation and for all recipients of liver, pancreas, and small bowel transplants [108].

Clinicians using fluconazole in solid-organ transplant recipients should be mindful of its inhibition of the cytochrome P450 system and monitor therapeutic drug levels accordingly.

Herpes Simplex Virus

Epidemiology and Pathophysiology

The esophagus is the most common site of visceral HSV infection among the immunocompromised [116] and the second most common esophageal pathogen (behind *Candida*) in the immunocompetent. In a study of >1300 consecutive autopsies, HSV esophagitis was identified in 1.8 %, the overwhelming majority of whom were

immunocompromised [61]. Males [61, 116], the HIV infected, and patients receiving antineoplastic, corticosteroid, or immunomodulator medications (e.g., solid-organ transplant recipients, inflammatory bowel disease patients) are more frequently afflicted. In case reports, HSV esophagitis has been associated with eosinophilic esophagitis. One hypothesis is that HSV-related mucosal damage may allow ingested allergens a portal of entry for sensitization [130]. Alternatively, treatment of eosinophilic esophagitis with topical fluticasone may predispose to HSV esophagitis [82].

HSV esophagitis may arise as a primary infection or as reactivation of disease latent in the neuroganglia. The virus has a tropism for stratified epithelium, and it has been suggested that this may explain why the esophagus is the preferred site in the gastrointestinal tract for infection [140].

Clinical Manifestations

The majority of patients present with an acute onset of esophageal symptoms including odynophagia (76 %), heartburn (50 %), dysphagia (21 %), and fever (24 %). They may experience a prodrome that may include fever, myalgias, and weight loss owing to decreased oral intake [116]. Concomitant orolabial lesions are uncommon in contrast to *Candida* esophagitis.

Diagnosis

At endoscopy, friable mucosa, discrete "volcano" ulcers, and exudates are seen in the mid and distal esophagus. Vesicles, if present, are typically confined to the upper third of the esophagus. The diagnosis is ascertained by histopathology, culture, and polymerase chain reaction (PCR). Brushings obtained from the ulcer edge are more likely to yield diagnostically helpful information in contrast to specimens from the center of the lesion, where few infected epithelial cells are present [146]. Microscopic findings include multinucleated giant cells, ballooning, and eosinophilic nuclear inclusions (Cowdry type A) limited to the mucosal layer. When typed, most HSV esophagitis is associated with HSV-1 [146].

Treatment

HSV esophagitis is self-limited in immunocompetent children. Treatment with intravenous acyclovir is undertaken when severe odynophagia or dysphagia precludes oral hydration and alimentation. Though controlled trials have not been conducted, most clinicians treat milder cases with oral acyclovir with the belief that the duration or severity of symptoms may be attenuated. Immunocompromised patients will not clear the infection themselves and treatment with acyclovir is indicated. Recurrent infections are uncommon in immunocompetent but may be encountered in the immunocompromised patient.

Cytomegalovirus

Epidemiology and Pathophysiology

In contrast to HSV, cytomegalovirus esophagitis has only rarely been described in the immunocompetent host. It is a ubiquitous virus; the vast majority of people are seropositive by late childhood or early adolescence. In those with intact immune function, an appropriate response is mounted upon initial exposure, and the virus becomes latent in the leukocytes. Like HSV, many cases of CMV esophagitis result from reactivation of latent infection under conditions of immunosuppression (e.g., HIV, immunomodulator medications).

Clinical Manifestations

The spectrum of presenting symptoms in CMV esophagitis depends largely on whether the episode represents primary infection or reactivation and which other parts of the gut are affected. CMV esophagitis is more likely to present with nausea, vomiting, fever, epigastric pain, and weight loss in addition to odynophagia and dysphagia than other esophageal infections; some speculate this is due in part to a viral syndrome that accompanies primary infection [9]. The onset of these signs and symptoms is generally more indolent than with HSV esophagitis. When CMV disease coexists in other parts of the gut, symptoms such as lower abdominal pain or diarrhea may predominate. It should also be

remembered that multiple pathogens may coexist in the immunosuppressed child.

Diagnosis

Serology is neither sensitive nor specific for CMV esophagitis. On upper endoscopy, there are classically large ulcers in the mid to distal esophagus with a linear orientation. Biopsies should be directed to the ulcer base because unlike HSV, CMV viral cytopathic effect is most prominent in the fibroblasts and endothelial cells rather than the squamous epithelium. Brushings add little to the diagnosis of CMV [143], and culture is also inferior to biopsy and immunohistochemical staining. Molecular diagnostics are increasingly available and attractive owing to their rapid turnaround time.

Treatment

Intravenous ganciclovir and foscarnet are equally efficacious and safe [109]; 2 weeks of treatment is advocated. Relapse is common among the profoundly immunosuppressed, and consideration should be given to prophylaxis until cell counts are restored (in the case of HIV) or immunosuppression can be liberalized (when iatrogenic). Routine serological testing of organ recipients and donors and targeted prophylaxis have reduced the incidence of transplant-associated disease.

Iatrogenic Esophageal Injury

Our ability to treat both complex and simple diseases has grown by leaps and bounds in the last century. And while these therapies are life enriching and prolonging, some can cause esophageal injury. From the pain reliever taken to assuage low-back pain to the chemotherapeutic agents used to condition for bone marrow transplantation, iatrogenic esophageal injuries are important and not infrequent complications of medical treatment.

Pill-Induced Esophagitis

Epidemiology and Pathophysiology

Pills are designed to deliver pharmaceutical compounds to the stomach or intestine; their inappropriate retention in the esophagus can result in injury. The widespread use of liquid medications for infants and children means that most cases of pill esophagitis occur in older children and adolescents. In adults, women are more often diagnosed with pill esophagitis than men, and this has been attributed to their increased exposure to frequently implicated pills [71]. Antibiotics (e.g., tetracycline, doxycycline), nonsteroidal anti-inflammatories (NSAIDs), ferrous sulfate, potassium chloride, and alendronate have repeatedly been associated with esophagitis in the medical literature.

Pill esophagitis can result from the caustic [13], hyperosmolar [71], or direct cytotoxic effect [71] of the medication on the esophageal epithelium. Risk factors for pill-induced esophagitis include pill characteristics (e.g., large size, sustained-release formulations, pill coating), patient characteristics (e.g., anatomical or motor anomalies of the esophagus), and administration characteristics (e.g., taking pills without a fluid bolus or before lying down) [48]. Experimental evidence suggests that substantial variability in the tendency of a pill to adhere to the esophagus exists among the same medication depending on the manufacturer [122]. This underscores the importance of the physical properties of a pill independent of its active ingredient.

Clinical Manifestations

Most often the patient will present with sudden onset of odynophagia, retrosternal burning pain, and dysphagia. Older children frequently volunteer that the onset of symptoms followed pill swallowing; the sensation of something stuck in the esophagus is not uncommon. Personal experience, however, suggests that this is seldom the case. Rarely, hematemesis can be the presenting symptom; this may be a clue to NSAID-induced esophagitis [2].

Diagnosis

In many cases, history will be sufficient to make the diagnosis. Contrast studies of the upper gastrointestinal tract are less sensitive than endoscopy to diagnose pill esophagitis but are the preferred modality to evaluate for a possible

anatomical predisposition to retained pills. Endoscopy usually reveals a discrete ulcer surrounded by normal esophageal mucosa. Occasionally remnants of the pill may still be adherent to the mucosa. Characteristically, like food bolus impactions, pill esophagitis occurs at areas of esophageal narrowing, low-amplitude contractile motility, or preexisting lesions (e.g., stricture, web, ring) [21]. Biopsies may be helpful to diagnose an underlying condition like eosinophilic esophagitis or gastroesophageal reflux disease (GERD)-related strictures.

Treatment

Though no trials have been conducted to evaluate their efficacy, most clinicians utilize histamine-2-receptor antagonists (H2RAs), proton pump inhibitors, or sucralfate to treat pill esophagitis. Where feasible, cessation of the offending pill or transition to a liquid form of the medication would prevent recurrence. Taking pills with an ample amount of fluid while standing or seated and remaining so for several minutes thereafter are good practices with evidence to support their routine implementation [13, 56].

Chemotherapy-Induced Esophagitis

Epidemiology and Pathophysiology

The prevalence of chemotherapy-induced esophagitis in children or adults is not known. Oral mucositis, on the other hand, is known to affect more than half of adults undergoing some chemotherapy regimens [128]. Esophageal disease is present in most of these patients [7], and it is cited among the most troubling symptoms experienced by patients receiving chemotherapy [12].

High rates of cell turnover predispose the entirety of the gastrointestinal mucosa to damage from chemotherapeutics. Though chemotherapy-induced mucositis can affect any portion of the gastrointestinal tract, its presence in the mouth and esophagus is an important determinant of complications including the need for parenteral nutrition, bacteremia, prolonged hospitalization, and interruption of therapy [127]. There is a dearth of literature that deals strictly with chemotherapy-induced esophagitis [128]. This may reflect the fact that it frequently coexists with much more readily observable oral mucositis [140] but may also indicate the complexity of teasing this entity apart from reflux disease and esophageal superinfection which are common in this population as well [146].

Risk factors for chemotherapy-induced esophagitis include the agent utilized, its dose and the frequency of its administration as well as concomitant radiation treatment. Conditioning regimens for autologous bone marrow transplantation as well as dactinomycin, bleomycin, cytarabine, 5-fluorouracil, methotrexate, and vincristine are commonly implicated in chemotherapy-induced mucositis [106].

Because chemotherapy is delivered systemically, its injury proceeds from the deeper basal layer through to the superficial epithelium. The primary event in chemotherapy-induced esophagitis is thought to be either endothelial dysfunction or DNA damage which activates cellular danger-signal pathways, the result of which is a feed-forward inflammatory loop culminating in ulceration [127, 129].

Clinical Manifestations

Dysphagia and odynophagia typically manifest within a week of starting chemotherapeutics and usually will resolve within 2 weeks after cessation of treatment. Coexistent oral mucositis may dominate the clinical picture, preventing oral alimentation and obscuring esophageal symptoms. A grave complication of esophageal mucositis is superinfection, usually with *Candida* [127] which can give rise to systemic fungemia, particularly in the neutropenic patient [7]. Case reports have indicated that esophageal strictures can be the presenting sign of upper gastrointestinal injury during chemotherapy in children [69].

Diagnosis

Awareness of the mucositic potential of specific chemotherapeutics and anticipation of this common side effect are usually sufficient for diagnosis. Superinfection with viral or fungal pathogens must be considered in the differential diagnosis, however. Endoscopy plays a minor role in

chemotherapy-induced esophagitis because patient factors (e.g., neutropenia, thrombocytopenia) usually tip the risk-benefit analysis against its application [146].

Treatment

Prevention of mucositis is an area of ongoing research [68, 127]. Adult guidelines published in 2007 by the International Society for Oral Oncology do not specifically address esophageal mucositis but recommend only that ranitidine or omeprazole be used for prevention of chemotherapy-induced epigastric pain [68]. This document is also specifically recommended against sucralfate for oral mucositis [68].

Because it is generally self-limited in nature [106], many experts treat esophageal mucositis expectantly with narcotic analgesics [128].

Radiation-Induced Esophagitis

Epidemiology and Pathophysiology

With advances in oncology, there are increasingly children who are treated for and who ultimately survive cancer. These data are evolving, but it is probably reasonable to infer that in the absence of preventive strategies, radiation esophagitis will continue to burden pediatric cancer survivors.

Radiation-induced esophageal injury can be categorized as acute and late [142]; each has a slightly different pathophysiology and presentation; therefore, they are discussed separately below. It should be noted that patients receiving radiation therapy are usually also at risk for infectious (particularly fungal or viral) esophagitis. Indeed both conditions may be present; therefore, the clinician should maintain a high index of suspicion.

Risk factors for radiation esophagitis include dose, schedule, and use of concomitant chemotherapy [33, 76, 85, 142].

Acute esophageal radiation toxicity typically manifests within 2 weeks of beginning treatment and is marked by capillary dilation and thrombosis, edema, and inflammation accompanied by endothelial proliferation [140, 142]. On the other hand, late radiation-induced esophageal injury comes to clinical attention weeks to months after cessation of treatment and tends to be referable to chronic inflammation and fibrosis of the lamina propria and submucosa giving rise to stricturing [140, 142]. Using clinically apparent strictures or perforations as endpoints, it has been estimated that 68–72 Gy delivered over one-third of the esophagus is necessary for 50 % of adult patients to develop these complications over 5 years [43]. Analogous data are not available for children.

Clinical Manifestations

Esophageal symptoms like dysphagia and odynophagia are almost universal among patients receiving radiation treatment that includes the esophagus in the therapeutic field [43, 148]. These symptoms in addition to retrosternal pain are characteristic of acute radiation esophagitis. Late-radiation esophagitis more frequently presents as only dysphagia which is usually related to esophageal strictures. On rare occasions, esophageal perforation or tracheoesophageal fistulae [76] complicate late-radiation esophagitis.

Diagnosis

Upper gastrointestinal contrast studies may demonstrate diffuse esophageal ulceration acutely and is sensitive for stricturing disease later. Disorganized peristalsis is frequently cited as a finding in late-radiation esophagitis [42]; however, at least one small adult study failed to document anomalous esophageal transit or motility in this setting [148]. Esophagogastroduodenoscopy has the benefit of allowing the physician to sample the esophagus (e.g., cytologic brushings, biopsy) and exclude coexistent *Candida* or viral esophagitis since these entities have considerable symptomatic overlap.

Treatment

There are no trials to substantiate the effectiveness of acid suppression, topical anesthetics (e.g., viscous lidocaine), diphenhydramine, or sucralfate, but they are routinely utilized. On the contrary, one placebo-controlled trial of sucralfate in adults beginning radiation therapy found no improvement in symptoms and a tenfold higher

rate of discontinuing the study treatment among those receiving sucralfate versus placebo [92].

When encountered, infectious esophagitis should be treated appropriately. Strictures are usually amenable to endoscopic dilation but may require several sessions to achieve clinically effective results [42, 76, 86].

Amifostine is a free radical scavenger that has been explored in adult studies to mitigate radiation and chemotherapy-induced esophagitis; some trials have shown benefit favoring its use [74, 75, 120], while others are equivocal [98]. Ongoing research seeks to establish the role for gastrointestinal-protective agents in the prevention of radiation-induced toxicity [15].

Esophageal Manifestations of Systemic Disease

Esophageal involvement occurs with many systemic diseases and can manifest as dysmotility or mucosal injury. The initial clinical presentation for these diseases may include esophageal symptoms, and therefore physicians should be familiar with the esophageal manifestations of various systemic diseases. The esophageal abnormalities associated with connective tissue diseases, cutaneous diseases, and neuromuscular disorders are described.

Connective Tissue Diseases

Scleroderma

Systemic sclerosis, the systemic form of scleroderma, is a multisystem disease of unknown etiology characterized by collagen deposition in the skin and internal organs [28]. Systemic sclerosis can be further classified into diffuse or limited, also known as progressive systemic sclerosis and CREST (calcinosis cutis, Raynaud's phenomenon, esophageal abnormalities, sclerodactyly, and telangiectasias) syndrome, respectively [28]. Childhood onset of systemic sclerosis is rare, representing less than 10 % of all cases. The male to female ratio is 3:1 for children 8 years of age or greater [149].

The gastrointestinal tract is commonly affected in both diffuse and limited systemic sclerosis [26]. Esophageal dysfunction, as revealed by diagnostic tests such as manometry, is present in 75–90 % of patients [27, 46, 104, 114]. The characteristic esophageal abnormalities include an incompetent lower esophageal sphincter (LES) and decreased smooth muscle peristalsis [27].

Symptoms of esophageal dysfunction are less prevalent and may be present in only 35–50 % of patients [67, 77, 136]. Dysphagia and symptoms of gastroesophageal reflux (GER) are the most common complaints [104]. Early satiety with resultant weight loss, regurgitation, and food impaction has also been reported [27, 104].

Diagnostic studies to assess for esophageal involvement include barium esophagrams, radionucleotide scintigraphy, esophageal manometry, and endoscopy [21, 104]. Barium esophagrams demonstrate esophageal dilation and reflux of contrast material into the proximal esophagus [21, 104]. Esophageal strictures can also be identified [104]. Diminished or absent peristaltic contractions can be visualized; however, in comparison to esophageal manometry, barium radiography is a less sensitive study for detecting motility abnormalities [21, 104, 141].

Radionucleotide scintigraphy is diagnostically useful to assess esophageal transit time and clearance [21, 67]. It is a noninvasive, sensitive, and an easy-to-perform test making it an ideal diagnostic modality to screen patients with systemic sclerosis for esophageal dysmotility. Esophageal manometry is needed for specific confirmation [21, 67].

Esophageal manometry is a highly sensitive test for esophageal dysmotility. As previously mentioned, in patients with systemic sclerosis, the characteristic findings on esophageal manometry include reduced LES tone and decreased frequency and amplitude of peristaltic contractions in the distal two-thirds, smooth muscle portion of the esophagus [21, 46, 47, 100, 125]. Of note, these findings are not limited to systemic sclerosis and may be seen less commonly in other rheumatologic disorders. The study is invasive and may cause discomfort to the patient; however, complications are rare [21].

Endoscopy is not utilized to diagnose esophageal dysfunction in patients with systemic sclerosis but to assess the mucosal damage that may occur as a consequence [104]. Mucosal changes consistent with reflux esophagitis can be seen in 60 % of patients with systemic sclerosis [104]. Chronic GER can result in columnar-cell replacement of the squamous cell layer of the esophagus, Barrett's esophagus [21, 66, 104]. This premalignant condition imparts an increased risk of adenocarcinoma; therefore, patients with Barrett's require careful endoscopic surveillance [21, 66, 104].

Currently, no treatment is available for the management of esophageal dysfunction in systemic sclerosis. Minimizing esophageal injury secondary to excessive esophageal acid exposure is the current standard of care [104]. Behavioral modifications include dietary changes (e.g., low-fat diet) and lifestyle changes (e.g., avoidance of smoking) [104].

Medical therapy consists primarily of inhibitors of gastric acid secretion, proton pump inhibitors and H2RAs, and prokinetic agents [104, 117, 124, 126]. Proton pump inhibitors when compared to H2RAs are more effective in reducing gastric acid secretion and improving mucosal changes secondary to GER [126].

Surgical management of GER is effective for the treatment of primary GER. In patients with systemic sclerosis, GER occurs secondary to esophageal dysfunction resulting from this progressive systemic disease [104, 134]. Patients with systemic sclerosis are at greater risk of complications related to general anesthesia and antireflux surgeries; therefore, surgery should be limited to patients with severe, intractable GER [104, 134].

Mixed Connective Tissue Disease

Mixed connective tissue disease (MCTD) is an overlap syndrome characterized by a combination of the clinical features of systemic lupus erythematous (SLE), systemic sclerosis, and polymyositis in addition to high serum titers of antibodies to the ribonucleoprotein component of extractable nuclear antigen, anti-RNP [123]. As in systemic sclerosis, esophageal dysfunction is common in MCTD. Esophageal symptoms include dysphagia, regurgitation, and symptoms of GER, but they are rarely spontaneously referred to by the patient [19, 32, 37, 53, 77, 89].

Characteristic esophageal manifestations in MCTD include LES incompetence and hypomotility of the smooth muscle portion of the esophagus [32, 37, 77, 89]. Total aperistalsis of the esophageal body may be seen in 17–53 % of MCTD patients [53]. Diminished upper esophageal sphincter (UES) pressure has also been variously identified in patients with MCTD; however, this abnormality has been observed in patients with polymyositis (PM) and SLE as well [53, 89].

It has been suggested that esophageal peristalsis in MCTD may improve with corticosteroid therapy [89, 111]. Evidence in support of this potential therapy is not definitive; therefore, further studies are needed to elucidate the benefit of corticosteroid therapy for the management of esophageal dysfunction in MCTD.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease of unknown etiology that can affect any organ system of the body. The clinical manifestations of SLE vary widely and have a relapsing and remitting course [8, 57]. SLE may affect up to 10–15 % of children and adolescents. The clinical presentation of SLE in children is as variable as in adults and occurs at any age with an increasing prevalence after the first decade of life [8, 57, 80].

Esophageal symptoms occur in 2–25 % of patients with SLE [25, 53]. Dysphagia is the most common esophageal complaint followed by symptoms of GER [53, 132]. These symptoms are frequently attributed to esophageal hypomotility; however, a poor correlation exists between the presence of esophageal symptoms and esophageal manometry abnormalities [22, 118]. Lower esophageal dysmotility is most common in patients with SLE; however, involvement of the

upper one-third of the esophagus has been reported [53, 77, 118]. Unlike patients with systemic sclerosis, LES hypotension is mild or absent [77]. Authors have suggested that moderate to severe decrease in lower esophageal pressure may help to differentiate between systemic sclerosis and SLE [77].

Several studies have investigated the association between esophageal dysfunction in SLE and the presence of Raynaud's phenomenon [53, 97, 131]. Early studies report a positive relationship and a potential correlation with high titers of hnRNP protein A1 antibodies [53, 97, 131]. The results of a more recent study, however, did not support the association of esophageal dysfunction in SLE and Raynaud's phenomenon [77]. Further studies are needed to clarify this relationship.

There are currently no specific treatment measures for esophageal dysfunction in SLE [132]. Supportive management of esophageal symptoms with inhibitors of gastric acid secretion, H2 receptor antagonists and proton pump inhibitors, and reflux precautions may be of benefit [132]. Treatment of active SLE would be predicted to improve symptoms of esophageal dysfunction; however, this has not been specifically studied.

Polymyositis/Dermatomyositis

Dermatomyositis and polymyositis are autoimmune myopathies caused by an inflammatory infiltration of the skeletal muscle [14, 30]. Dermatomyositis is a complement-mediated small vessel angiopathy, while polymyositis involves a direct T-cell-mediated invasion of myocytes [14, 30]. Both are characterized by a proximal myopathy; however, patients with dermatomyositis also manifest cutaneous changes including heliotrope rash of the eyelids, erythroderma, and telangiectasias [39, 115].

In children, juvenile dermatomyositis is the most common inflammatory myopathy [91, 115]. The peak incidence is from 5 to 10 years of age, and girls are affected more often than boys. Juvenile polymyositis rarely occurs before the second decade of life and therefore accounts for only 3–6 % of juvenile inflammatory myopathies [94, 105, 110, 133].

The striated muscle of the pharynx, upper esophageal sphincter, and proximal esophagus are commonly affected in patients with inflammatory myopathies [35, 39, 44, 62]. Dysphagia is the most common gastrointestinal symptom. Other complaints include symptoms of GER, nasopharyngeal regurgitation, and aspiration [62, 107].

Diagnostic studies to evaluate proximal esophageal dysfunction include cine-esophagram and esophageal manometry [34, 77]. Radiographic findings demonstrate prolonged pharyngeal peristalsis, nasopharyngeal reflux, vallecular pooling of barium, and tracheal aspiration [39, 62]. Characteristic manometric abnormalities include decreased cricopharyngeal sphincter pressure and diminished pharyngeal and proximal esophageal peristaltic contractions [34, 77].

Smooth muscle dysfunction of the esophagus has also been described in patients with inflammatory myopathies [58]. Manometric findings include decreased LES tone and low-amplitude peristaltic contractions of the distal esophagus. Delayed esophageal emptying is another notable finding suggesting involvement of the smooth muscle portion of the esophagus [58]. The presence of delayed esophageal emptying has been shown to correlate with the severity of proximal muscle weakness [34, 62].

Corticosteroids are the initial treatment of choice for polymyositis and dermatomyositis [30]. Immunosuppressive medications are reserved as a second-line agent for patients with steroid-refractory inflammatory myopathies. Incidental improvement of esophageal symptoms with these therapies has been reported; however, there are no controlled clinical trials demonstrating their direct efficacy on esophageal dysfunction [39]. Intravenous immunoglobulin was found to be an effective therapeutic agent for patients with severe, steroid-resistant esophageal dysfunction in a double-blind placebo controlled trial [31, 88].

Other treatment options include medical therapy for GER symptoms with inhibitors of gastric acid secretion, H2 receptor antagonists

and proton pump inhibitors, as well as swallowing rehabilitation for dysphagia. Controlled clinical studies assessing the effectiveness of these interventions have not been conducted [21].

Cutaneous Diseases

The esophagus can be affected in various dermatologic diseases. Esophageal involvement may occur because the epithelium of the skin and upper one-third of the esophagus are both comprised of stratified squamous epithelium. The primary dermatoses include epidermolysis bullosa, bullous pemphigoid, and pemphigus vulgaris. Esophageal involvement of epidermolysis bullosa is discussed in detail in a later chapter. Bullous cutaneous lesion with involvement of the esophageal mucosa is also characteristic of Stevens-Johnson syndrome; therefore, it is covered in this chapter.

Bullous Pemphigoid

Bullous pemphigoid is an autoimmune disease characterized by bullous lesions [3, 10, 21]. The targeted antigens are components of the basement membrane zone of the skin, bullous pemphigoid antigen 1 (BPAG1) and 2 (BPAG2) [21, 84]. It rarely occurs in children and usually affects the elderly. The characteristic clinical manifestation is a widespread cutaneous bullous eruption involving the flexural areas, axillae, and groin [10]. Infants can have more pronounced involvement of their palms, soles, and face [10]. Oral and esophageal bullae present less frequently since mucous membrane involvement is not common. Oral lesions do tend to occur more frequently in children than adults [10].

Cicatricial pemphigoid is a variant of bullous pemphigoid characterized by more extensive mucosal membrane involvement and less cutaneous lesions [4, 21]. Esophageal involvement occurs in 5 % of patients and manifests as esophageal bullae, webs, and strictures secondary to scarring [4, 21, 99].

Endoscopy can be used to identify esophageal bullae but may cause further injury to the esophageal mucosa [21, 144]. Direct immunofluorescence of esophageal biopsies reveals immunoglobulin G (IgG) and complement (C3) deposition in the basement membrane [21, 139].

Systemic corticosteroids are the initial treatment for esophageal involvement in both bullous pemphigoid and cicatricial pemphigoid [21, 139]. Steroid-sparing immunosuppressive medications are also effective treatment options [11, 21, 55, 73, 93].

Pemphigus Vulgaris

Pemphigus vulgaris is also an autoimmune disease characterized by bullous lesions on the skin and mucous membranes [5, 6, 102]. The target antigen is desmoglein 3, an adhesion protein for keratinocytes in the epidermis [5, 6, 36, 102]. It occurs more commonly in children than bullous pemphigoid but is still rare [21]. Mucous membrane involvement is also more marked. Oral mucosal lesions are usually the initial clinical manifestation followed, up to several months later, by widespread cutaneous bullous lesions involving primarily the face, trunk, pressure points, groin, and axillae [10, 49, 51, 102]. Mucous membrane involvement can extend into the esophagus from the oral cavity. Patients with esophageal lesions tend to be asymptomatic but may complain of dysphagia, odynophagia, and hematemesis [41, 49, 50, 63, 119, 135, 145, 147]. A rare esophageal complication of pemphigus vulgaris is sloughing of the entire mucous membrane resulting in the formation of an esophageal mucosal cast, esophagitis dissecans superficialis [64, 121].

As with bullous pemphigoid, endoscopy can be used to evaluate the appearance of the esophageal mucosa and obtain biopsy specimens [18, 21, 45, 135]. Acantholytic blisters on direct immunofluorescence of esophageal biopsies confirm the diagnosis of esophageal pemphigus vulgaris [18, 21, 41, 102, 135].

High-dose systemic corticosteroids are used to initially treat and achieve disease

remission [16, 17, 18]. Steroid-sparing immunosuppressive medications are useful options for maintenance regimens [16, 18, 20].

Stevens-Johnson Syndrome

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe immune-mediated hypersensitivity reactions characterized by fever and mucocutaneous lesions [78, 81]. Cutaneous lesions can progress to epidermal necrosis and sloughing [78, 81]. Medications and infections, in particular *Mycoplasma pneumonia* and herpes viruses, are the leading precipitating factors for SJS and TEN in children [78, 81].

Clinically, esophageal involvement can manifest as bullous lesions and erosions of the mucosa. Mucosal scarring can lead to esophageal web and stricture formation [52, 59, 87, 90].

Treatment involves immediate discontinuation of potential triggering medication or identification and treatment of underlying infection. Further care is supportive and symptomatic (e.g., intravenous hydration, nutritional support, and pain management) [21, 78, 81].

Neuromuscular Disorders

Chiari Malformations

Chiari malformations are a structural defect of the brain characterized by caudal displacement of the cerebellar tonsils through the foramen magnum [113, 140]. Esophageal abnormalities reportedly occur in 5 % of patients with a Chiari malformation as a result of brainstem dysfunction [112, 113, 140]. Clinical manifestations include dysphagia, nasal regurgitation, tracheal aspiration, and symptoms of GER. Dysphagia may be the initial presenting symptom of brainstem dysfunction in patients with Chiari malformations [112, 113].

Diagnostic modalities to evaluate esophageal dysfunction include barium esophagrams and esophageal manometry [17]. Radiographic findings include delayed transit time through a narrowed cricopharyngeus and pharyngonasal regurgitation [112, 113]. Esophageal manometry is more sensitive and can identify UES dyscoordination or failure of the UES to completely relax [112, 113].

Treatment of esophageal dysfunction in patients with Chiari malformations involves treatment of the malformation to improve brainstem function, usually with craniocervical decompression [113].

Myotonic Muscular Dystrophy

Myotonic muscular dystrophy (OMIM 160900) is a rare form of muscular dystrophy. It is an autosomal dominant disorder with variable penetrance characterized by myotonia, muscle wasting, frontal baldness, cataracts, and cardiac heart block or arrhythmia. Disease presentation is usually during adulthood; however, childhood onset has been reported [140].

Pharyngoesophageal dysfunction occurs in the majority of patients; however, clinical symptoms are present in less than 50 % of patients [40, 79, 103]. Dysphagia is the most common complaint followed by symptoms of GER and regurgitation [96, 103].

Pharyngeal and esophageal dysmotility can be demonstrated utilizing barium esophagrams and esophageal manometry [29, 72]. Esophagram findings include barium stasis in the pharynx, prolonged esophageal transit time, and a dilated esophagus [29, 103]. Manometry reveals diminished UES tone and amplitude of peristaltic contractions in the striated and smooth muscle portions of the esophagus [29, 72, 79, 96, 103].

Myasthenia Gravis

Myasthenia gravis is an autoimmune neuromuscular disease caused by autoantibodies directed against the acetylcholine receptor (AChR) at the neuromuscular junction [29, 38]. It is characterized by striated muscle weakness and fatigability [29, 38]. Involvement of the striated muscle portion of the esophagus clinically manifests as

dysphagia [70]. Patients are generally able to chew and swallow without difficulty at the beginning of a meal; however, as the meal progresses, chewing and swallowing become more labored secondary oropharyngeal and esophageal muscle fatigue [83, 140].

Esophageal manometry demonstrates diminished peristaltic contractions, primarily in the upper esophagus, and prolonged peristaltic waves [60]. Esophageal weakness may only become evident after a few swallows. Both clinical and manometric features tend to improve with rest or treatment with anticholinesterase medication [60, 140].

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Oesophageal Varices

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P.J. McKiernan

Oesophageal varices are dilated submucosal veins usually found in the lower oesophagus which develop as a result of portal hypertension. Portal hypertension in turn is usually due to cirrhosis but can have a presinusoidal cause such as extrahepatic portal vein obstruction (EHPVO) or congenital hepatic fibrosis, the important distinction being that liver function is preserved.

Within the oesophagus there are four layers of veins, intraepithelial channels, a deeper superficial venous plexus, deep intrinsic veins and then the perforating veins through which blood drains into the perioesophagus and from there to the azygous veins. The arrangement is different in the palisade zone of the lower 4–5 cm of the oesophagus. Here vessels are arranged longitudinally in the superficial venous plexus and flow can be bidirectional [33].

If the hepatic venous pressure gradient (HVPG) is >10 mmHg, pressure is transmitted through the left gastric vein, and valves in the perforating veins become incompetent allowing retrograde flow into the deep intrinsic veins and their tributaries. These deep intrinsic veins dilate and assume a subepithelial position to become major variceal channels. In the palisade zone, in addition to the pressure from the perforating veins, there is also increased cephalad flow from the stomach [20].

Once established, varices usually increase in size unless the cause of portal hypertension can be corrected. Variceal bleeding occurs where the combination of large variceal diameter, decreased wall thickness and increased intraluminal pressure raise variceal wall tension beyond a tolerable threshold [20].

There have been no systematic prospective endoscopic studies of unselected groups of children with cirrhosis or portal vein thrombosis. Hence incidence studies have been derived from cross-sectional studies from large specialist centres. These show a high incidence of varices developing quickly in cirrhosis, with rates in children with biliary atresia ranging from 40 to 70 % [30, 45] usually before the age of 5 years. In cystic fibrosis-associated cirrhosis [9], nearly 90 % of those with cirrhosis developed oesophageal varices, on average 3 years after the first signs of liver disease. Varices are even more common in children with EHPVO [46].

The diagnosis of oesophageal varices still depends on upper GI endoscopy [40]. There have been attempts to develop clinical predictors of oesophageal varices [14], but none have yet been prospectively evaluated. Partly because of the lack of evidence for primary prophylaxis, there are no widely used guidelines for which children with portal hypertension should undergo diagnostic endoscopy, and hence there are wide variations in practice. In our centre we undertake

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diagnostic endoscopy in all children who present with, or develop splenomegaly for the first time. Children who have oesophageal varices are then given individual plans for what to do if they should have a gastrointestinal bleeding.

At endoscopy, the size of varices and the presence of red colour signs should be recorded. A simple classification of varices into small and large is used in adult practice [7], but a variety of grading schemes are used in children. There is a need for prospective validation of these schemes and to determine whether there is acceptable interobserver consistency.

Endoscopic ultrasound is as effective as videoendoscopy for detecting oesophageal varices but has the added advantages that variceal wall thickness can be measured, and paraoesophageal varices and feeding perforating veins can be recognised. The use of miniprobe systems means the technique can be applied even to small children during videoendoscopy [26].

Risk of First Variceal Bleeding

The 2-year bleeding risk in adults with cirrhosis and at least moderate large varices is 25–30 %. Lifelong risk of variceal bleeding is close to 50 % [6]. An increased bleeding risk in childhood is associated with increased variceal size [2], red colour signs seen at endoscopy [2] and severity of liver disease [30, 45]. Combining data from a number of paediatric studies reveals an overall risk of 22 % for variceal bleeding in children with cirrhosis, and 38 % in those with cirrhosis known to have oesophageal varices, over a mean follow-up of 5 years [2, 9, 27, 30, 45]. Age at first bleeding is related to the cause of cirrhosis, occurring at a mean age of 3 years in biliary atresia [27, 30] and 11.5 in cystic fibrosis [9]. In the single paediatric study reporting serial endoscopic findings, where signs of portal hypertension progressed, one-third bled over a 3-year follow-up [2].

In portal venous obstruction, the bleeding rate is even higher than in cirrhosis. The lifelong risk of bleeding is 80 % with 50 % of bleeds occurring before age 5 [46]. Although there is an impression that bleeding rate falls with time, this is not consistent, and first bleeding may occur in adult life.

Pressure measurements have an established utility in adult practice. A threshold for HVPG of 10 mmHg is necessary for varices to develop and 12 mmHg for variceal bleeding to occur [15]. There is little experience with HVPG measurement in paediatric portal hypertension, and it requires general anaesthesia and technical expertise. Information from paediatric TIPS suggests that the threshold of 12 mmHg may also apply to children [18, 40].

Primary Prophylaxis

Primary prophylaxis is a standard of care for adults with at least moderate oesophageal varices. Two methods are established, β-blockade and endoscopic band ligation (EBL). Nonselective β-blockers have a combined effect; the β_1 effect causes a decrease in cardiac output, and β_2 stimulation has a splanchnic vasoconstrictive effect which results in a fall in variceal pressure and in collateral blood flow [20]. The relative cost-effectiveness, tolerability and effectiveness of these have been the subject of numerous studies. Current guidelines for adults state that both interventions are acceptable prophylactic therapy, with β-blockers generally preferred as first-line therapy, and EBL reserved for patients in whom β-blockers are contraindicated or poorly tolerated [7, 16].

There have been no randomised controlled trials of β-blockers for primary prophylaxis in children. There are three observational studies published which reported 75 children, not all of whom underwent pretreatment endoscopy [10, 31, 39]. Treatment was generally well tolerated but overall 20 % bled, with a 30 % bleeding rate in those with more advanced liver disease.

There has been one controlled trial of endoscopic prophylaxis in children which used sclerotherapy [17], which can no longer be recommended. There have been three observational studies of EBL in children reporting 50 children treated [4, 5, 36]. The treatment was safe and effective with only two children bleeding during follow-up. However, these studies were uncontrolled, so at

present primary prophylaxis cannot be recommended outside of a clinical trial or protocol. Pragmatically, postpubertal children may be treated according to the adult guidelines, but for younger children, there is an urgent need for definitive trials in this area.

Acute Variceal Bleeding

This is the most feared complication of portal hypertension and the commonest cause of severe gastrointestinal bleeding in children [40]. This usually presents acutely with haematemesis or melaena but may present more subtly with anaemia. There is often a history of respiratory tract infection or other minor illness and occasionally nonspecific abdominal pain.

In adult patients, the 6-week mortality following an acute bleeding has improved but is still 20–30 % [7]. The mortality in children with cirrhosis is lower but still significant with reported death rate of 5–19 % [11, 45, 47]. The mortality is very low in portal venous thrombosis but deaths can still occur in this group [46]. Success of treatment requires control of initial bleeding episode, preventing rebleeding and managing the underlying disease.

Children should be admitted to hospital, stable intravenous access established and samples taken for haemoglobin, coagulation profile, electrolytes, blood and urine culture and 70 ml/kg blood crossmatched. A nasogastric tube should be passed in almost all cases. The risk of variceal trauma is minimal, and this allows removal of residual gastric contents and blood, which untreated predispose to aspiration, encephalopathy and ongoing bleeding. In addition this allows the early detection of ongoing or renewed bleeding.

Blood and colloid should be transfused to achieve normal heart rate and blood pressure while maintaining a CVP of 5 mmHg and haemoglobin in the range of 7–9 g/dl. Overtransfusion should be avoided, and only severe coagulation disturbance and thrombocytopenia should be corrected.

Antibiotic prophylaxis has been shown to decrease mortality in adults, so an appropriate antibiotic such as ceftriaxone or ciprofloxacin should be prescribed [40].

Pharmacotherapy for Acute Variceal Bleeding

Evidence from adult practice suggests that pharmacotherapy should be started immediately, for 2–5 days and that this complements endoscopic treatment [1, 7]. Two drugs are suitable for paediatric use, octreotide or Glypressin. Vasopressin is now obsolete and somatostatin is difficult to source.

Octreotide is a synthetic octapeptide which has been shown to be superior to vasopressin with less side effects. This has emerged as the preferred vasoactive drug in paediatric practice, probably reflecting the ready availability of a suitable preparation, familiarity with the product for other indications and its ease of use and safety. Paediatric observational studies have shown it to be effective and safe with early control of active bleeding in most cases [11, 41]. However, it should not be relied on as sole therapy as early rebleeding is likely [24]. The most common dosage regimen appears to be 1 μg/kg by slow bolus followed by infusion at 1–3 μg/kg/h.

Terlipressin

This is a synthetic analogue of vasopressin which has an immediate intrinsic vasoconstrictive effect followed by a sustained portal haemodynamic effect as it is converted to vasopressin. This is the only drug that has been shown to reduce mortality when used in variceal bleeding as a sole therapy. Reported side effects are similar to vasopressin but less frequent and severe.

There are no studies on the use of terlipressin in paediatric practice. Personal experience has shown this drug is much better tolerated than vasopressin. There are no specific dose recommendations for paediatrics, and it has been used pro rata to the adult regimen of 2-mg IV followed by 1–2 mg every 4–6 h for 72 h.

Endoscopic Treatments

Therapeutic endoscopy should be carried out as soon as possible once the patient is haemodynamically stable, and under general anaesthesia using an endoscope with the largest operating channel that can be safely passed. The exact timing of endoscopy will depend on local facilities, and my own practice is to undertake this on the next available daytime list unless there is ongoing bleeding when it is carried out immediately.

Injection sclerotherapy has been used in paediatric practice for more than 50 years [12]. The principle is that bleeding is stopped either by inducing thrombosis in the varix, or by compressing the varix by the inflammatory reaction occurring when sclerosant is injected around the varix. In chronic use, this inflammatory response leads to fibrous obliteration of the variceal channels. A variety of sclerosants have been used with nothing to choose between them. The largest experience in paediatrics is with 5% ethanolamine oleate [23].

The injection is carried out via the operating channel of a flexible endoscope using single-use injectors with retractile needles. Endoscopes with working channels down to 2.2 mm may be used with modified equipment. If a bleeding varix is identified, this should be treated immediately. It is usually easy to recognise where bleeding had originated, but even if no stigmata of current or previous bleeding is found, treatment should usually be commenced, so long as no other obvious site for bleeding exists and the varices are large. Injections are started just above the gastroesophageal junction and may be intra- or paravariceal. All varices at this level should be treated, with 1–3 ml of sclerosant being used per injection, then repeated if necessary to all varices 3–5 cm caudally. No more than 10–15 ml of sclerosant should be used per session depending on patient size. Varices more than 5 cm from the gastroesophageal junction should not be treated unless actively bleeding.

Sclerotherapy is very effective, with control of acute bleeding in 90% of cases [23, 40]. Complications are more likely following emergency sclerotherapy and include bleeding from ulceration, mediastinitis, oesophageal perforation, chylothorax and pneumothorax. There is a reported procedural mortality of approximately 1% [19].

EBL was first reported in humans in 1989 as an adaptation of treatment established for haemorrhoids [44]. A hollow cylinder with prestretched rubber bands is attached to the front of an endoscope. The variceal column is directly sucked into the hollow cylinder, and a band is released around the base of the varix. Acute bleeding is stopped by strangulation of the varix at the bleeding site. Over the next few days, ischaemic necrosis of the mucosa and submucosa develops; the rings are sloughed leaving shallow mucosal ulceration. Epithelialisation occurs within 2–3 weeks, and the submucosal vascular layers are replaced by maturing scar tissue by 8 weeks.

An initial control endoscopy is carried out to recognise bleeding points and to document the distance to the gastroesophageal junction to help prevent inadvertent banding in the stomach. The multiband apparatus is loaded onto the endoscope, which should have an external diameter of at least 8.6 mm to ensure a secure fit, and then repassed as far as the gastroesophageal junction. The endoscope is placed against the most distal variceal column and suction applied. When the varix fills the cylinder, the tripwire is pulled by turning the wheel and the endoscope pulled back. Care must be taken, especially in small children, that the oesophageal wall is not aspirated into the cylinder. Subsequent bands are applied in a proximal direction to variceal columns in the lower 5–6 cm of the oesophagus. An oesophageal overtube is no longer necessary and 2–6 bands may be used per session. I tend to restrict this to four per session as using more than this is often uncomfortable for the patient. As more bands are fired, visibility progressively improves and some manufacturers insert a coloured band to remind the operator when a single band remains. Banding is much better tolerated than sclerotherapy. 10–15% of children complain of transient retrosternal pain, but oesophageal stricture has not been reported in the paediatric literature.

EBL is now the preferred technique for managing acute variceal bleeding in adults. The published paediatric literature suggests that EBL is very effective in children with active bleeding [4, 13, 25, 29, 34, 36]. A major advantage compared to sclerotherapy is that once the bleeding point is ligated, bleeding control with improved visibility is almost immediate. However, banding equipment has not been extensively modified for paediatric practice, and it will not be possible to pass the loaded apparatus in some small children; hence, both endoscopic modalities should continue to be available in the management of acute bleeding.

Following endotherapy, patients should fast for at least 2 h, and solid feeding withheld until liquids are tolerated. Sucralfate should be given for 5 days as this appears to decrease the risk of early rebleeding.

Detachable nylon miniloops, which are tightened around the base of the varix and detached, or a clipping apparatus (Olympus HX-3 L) where a metal clip is placed directly across the varix has been used in a small number of children [28]. Both techniques are carried out through the working channel and have the advantage that they can be carried out without removing the endoscope and can in theory be used with smaller endoscopes than can band.

Treatment Failures

Initial failures with combined pharmacological and endoscopic therapy are usually best managed by a second attempt at endotherapy, but the use of TIPS may be considered depending on local expertise and facilities.

Transjugular Intrahepatic Portosystemic Shunting (TIPS)

This is a radiologically created portosystemic shunt. Via the transjugular route, a tract is created between branches of the hepatic and portal veins. This is dilated and a self-expanding stent inserted along the tract. This has the clear advantage of much less morbidity than a surgical shunt and little compromise to future liver transplantation.

There are no randomised studies of TIPS in acute bleeding, but cumulative adult experience has shown this to be possible in >90 % of cases when used as rescue therapy for bleeding resistant to endoscopic and pharmacotherapy [3]. Limited but increasing experience in paediatrics has been similar, i.e. it is not a primary treatment but is a very useful rescue option [18, 40].

The most common complication of TIPS is shunt stenosis or thrombosis with subsequent rebleeding, but this complication has been reduced by the development of polytetrafluoroethylene-covered stents. Proactive surveillance with ultrasound and venography can maintain patency rates of >90 % at 1 year. As with any portosystemic shunt, encephalopathy is possible. However, this has been less of a concern in paediatric practice and has usually been easily managed.

Recombinant factor VIIa has no role in the routine management of variceal bleeding but has been safely used in intractable cases with acceptable safety [21].

Balloon tamponade is highly effective and has been shown to control bleeding in up to 90 % of patients, but there is a rebleeding rate of >50 % when the balloon is deflated [20]. The Sengstaken-Blakemore tube is usually used. This single unit consists of a gastric and an oesophageal balloon with oesophageal and gastric suction ports. The tube is passed and the gastric balloon inflated in the stomach. Moderate traction to impact the gastric balloon at the gastroesophageal junction is usually sufficient to control bleeding, but on occasion the oesophageal balloon must be inflated. The position of the gastric balloon should be confirmed radiologically or endoscopically. The major complications relate to inflation of a misplaced gastric balloon, oesophageal and gastric mucosal necrosis and ulceration and aspiration.

Balloon tamponade should only be used in an intubated and sedated child where there is failure to control active bleeding, as a bridge to definitive treatment or to facilitate transfer to a specialist centre [40].

Emergency Surgery

Liver transplantation will be the eventual definitive treatment for most children with cirrhosis and portal hypertension. However the decision regarding liver transplantation should be based on the severity of the liver disease rather than portal hypertension per se. Emergency liver transplantation is rarely necessary and if carried out soon after bleeding carries a higher mortality [42]. In general, patients who are candidates for transplantation should be managed conventionally with pharmacotherapy and endoscopic treatment, followed by planned elective transplantation. In view of the risks of sclerotherapy-induced ulceration following transplantation [48], EBL is the preferred option in those awaiting transplantation [35]. For those with better-compensated liver disease, emergency rescue surgical procedures such as a mesocaval shunt or oesophageal devascularisation are now very rarely necessary given the above armamentarium.

Following a variceal bleed in children, subsequent recurrent bleeding rates are as high as 80 % [23, 40]. Hence all children surviving a variceal bleed should receive secondary prophylaxis [40].

Techniques for Secondary Prophylaxis

(a) Endoscopic treatment
(b) Pharmacotherapy
(c) Shunts – TIPS
- Mesoportal bypass
- Portosystemic shunts

Endoscopic Treatment

Adult studies have established that EBL is the preferred endoscopic method for secondary prophylaxis. Compared to sclerotherapy, there is improved survival, less rebleeding, fewer complications and fewer treatment sessions needed for eradication of varices [7]. The cumulative evidence confirms that EBL is also the preferred method in children [40]. A single randomised trial has shown the superiority of EBL to sclerotherapy in children with EHPVO [49]. In addition, seven observational paediatric studies [4, 13, 25, 29, 34–36] of variceal banding in 96 subjects with mean follow-up of 27 months show varices were eradicated in 80 % with fewer treatment sessions (means 3.2 vs. 5.2), less bleeding and fewer complications than sclerotherapy.

EBL is usually carried out at monthly intervals until variceal ablation, followed by control endoscopies at 6–12 monthly intervals. Recurrent varices should be ligated if they are bigger than grade 1. EBL can safely be undertaken as a day case [25].

Pharmacotherapy

β-blockers have been shown to be as effective as EBL for secondary prophylaxis in adults. The effects of both treatments are additive and current adult guidelines recommend combination treatment [16]. The efficacy of β-blockade can be improved if treatment is titrated to the HVPG gradient. In those in whom it falls to <12, the risk of rebleeding is close to zero, and where the HVPG falls by >20 %, the rate is <10 %. Therefore the consensus in adult practice is that HVPG should be used to titrate β-blockade [15].

Propranolol has been shown to successfully lower portal pressure in children [32], but there is limited therapeutic experience in paediatrics with just three uncontrolled trials. Of 23 children treated, 11 (48 %) bled during a 3-year follow-up. In those with more advanced disease, the bleeding rate was 70 % [10, 31, 39]. In contrast to adults, there is no evidence that the addition of propranolol improves the efficacy of endoscopic treatment in children [10, 43].

Propranolol is usually started at 1 mg/kg/day with the dose initially increased every 2 days until there has been a 25 % decrease in the heart rate or until the heart rate falls to a predetermined minimum value. In the published studies, doses of 1–8 mg/kg/day have been used, and it has

apparently been well tolerated. There were no reports of children who did bleed failing to mount an appropriate tachycardia. In adult practice, approximately 15–20 % of patients will be intolerant of β-blockers, and it is likely this will be similar or greater in childhood. As a result, propranolol cannot be recommended for routine secondary prophylaxis in children.

New drugs such as carvedilol, a β-blocker with intrinsic α-blocking properties, and losartan may represent a step improvement over propranolol but have not yet been studied in children. Nitrovasodilators cannot be recommended in children.

TIPS

Studies of TIPS as secondary prophylaxis compared to endoscopic treatment in adult practice have consistently shown a lower bleeding rate with TIPS at the cost of more encephalopathy, but no difference in overall mortality. The current consensus is that endoscopic and drug treatments are preferred, with salvage by TIPS if these fail [15].

The place of TIPS in acute bleeding in paediatric practice is summarised above. The same considerations apply to use for secondary prophylaxis; it is best reserved for failed endoscopic treatment as a short-term bridge in candidates for liver transplantation [40]. Technical developments such as polytetrafluoroethylene-covered stents may however change this balance, and in individual cases, this may be an excellent option where expertise exists.

Mesoportal Shunt

This recently developed physiological shunt has been developed for the treatment of EHPVO [8]. The procedure depends on patency of the superior mesenteric vein (SMV) and the umbilical branch of the left portal vein. A natural vascular graft (usually from internal jugular vein) is placed between the SMV and the umbilical branch of the portal vein, hence restoring physiological portal blood flow.

The medium term results of this surgery are excellent with complete protection against bleeding. A positive effect on treatment of hypersplenism, correction of coagulopathy and restoration of liver volume is obvious within months. Additionally, there is improved growth, better fluid cognitive ability and reversal of encephalopathy related to portosystemic shunting. These benefits are maintained for at least 8 years, and increasingly this operation is seen as curative for EHPVO [37]. A recent consensus statement recommended that this is the treatment of choice for children with EHPVO [46]. All affected should be assessed for feasibility of mesoportal bypass, and where it is feasible, it should be considered in all cases, even prior to the development of clinical complications. Any portal hypertension-related complication in EHPVO is now an absolute indication for mesoportal bypass where feasible [46].

Portosystemic Shunts

Any of these will result in a decrease in portal pressure, but also to a greater or lesser extent diversion of blood from the liver, with the risk of encephalopathy, hepatic atrophy and deterioration, and hepatopulmonary syndrome [20].

There are no randomised controlled trials of portosystemic shunts for secondary prophylaxis in paediatric practice, but previous experience shows high complication rates if they are done in cirrhotic children [2, 22]. These are usually only indicated in those with presinusoidal portal hypertension, where the mesoportal bypass is not feasible and/or endoscopic treatment has failed or is not available. In current practice, this should amount to no more than 10–15 % of affected patients [23].

The largest experience is with side-to side splenorenal shunt and mesocaval shunts. In skilled hands, these procedures are extremely well tolerated with a very low incidence of encephalopathy, and >90 % prevention of recurrent bleeding can be achieved [22, 38]. However, the risk of encephalopathy is lifelong; hence, all other alternatives should be first considered before embarking on this course (Fig. 64.1).

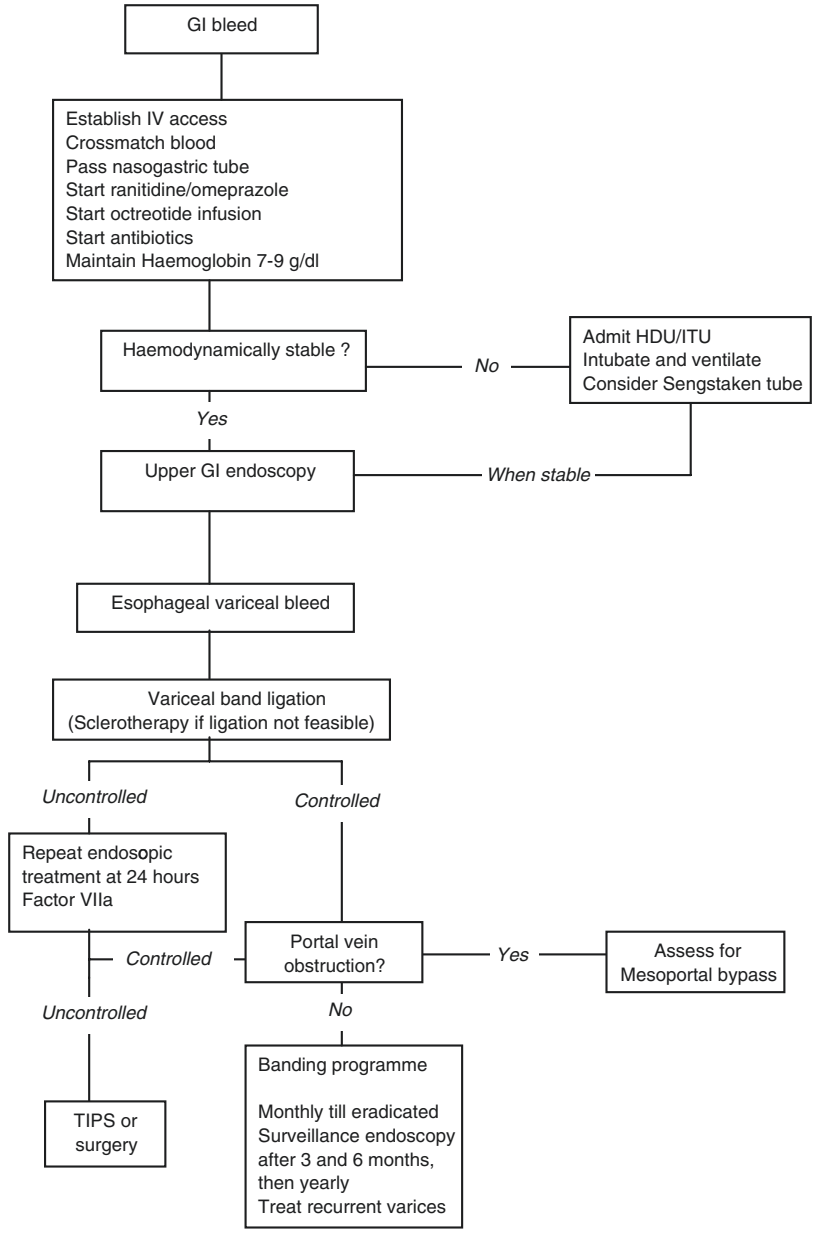

Fig. 64.1 Management of variceal bleeding in children

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Laparoscopic Heller-Dor Procedure for the Treatment of Esophageal Achalasia

65

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Introduction

Esophageal achalasia (EA) is a rare functional disorder of the esophagus characterized by abnormal motility of esophageal body (non-peristaltic waves) associated with incomplete, delayed, or absent relaxation of the lower esophageal sphincter (LES) [1]. The incidence is about 0.3–11/10^6/year with a prevalence of about 80/10^6 inhabitants. Only 5% of the patients suffering from this disease are younger than 15 years of age [2, 3].

Although EA is usually considered an acquired esophageal motility disorder, several studies suggested that genetic background may play a role, in children at least. Because the cause of achalasia remains unknown and there is no cure, treatment is aimed at relief of symptoms. The pathogenesis remains controversial; however the abnormal esophageal motility in EA seems to result from defects or imbalance between the excitatory and inhibitory neuromuscular transmitters [4–9].

Many different treatments have been proposed: pharmacological treatments (calcium channel blockers, such as nifedipine, sildenafil, or isosorbide dinitrate), pneumatic dilatations, removable self-expanding metal stents, and injection of botulinum toxin [10–15]. However these do not provide satisfactory long-term relief from symptoms of achalasia: the results are transitory, and repeated treatments are frequently required. The only way to definitively relieve symptoms is surgery. In 1914, Heller described an anterior/posterior myotomy for the treatment of "cardiospasm" [16]. Later on, Zaaijer et al. proposed an anterior myotomy alone for the same purpose. These techniques should be associated with a fundoplication, aimed at avoiding postoperative GERD and protecting esophageal mucosa. A partial anterior fundoplication according to Dor is the most effective in reducing the risk of stenosis or recurrence of achalasia and in preventing reflux. Laparoscopic modified Heller-Dor procedure is therefore the treatment of choice for EA.

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Indication for Operation/Workup

Symptom onset of EA is variable. Almost all the patients present with fluid dysphagia ("paroxysmal dysphagia"), retention, and regurgitation of undigested food; these findings should not be confused with vomiting. Chest pain is described in up to 40 % of patients. Failure to thrive and halitosis are associated symptoms along with nocturnal cough or repeated pneumonia related to pulmonary inhalation [17].

Achalasia may be associated with Allgrove's syndrome, an autosomal recessive familial condition characterized by adrenocortical insufficiency, alacrima, and esophageal motor dysfunction (also called ALADIN syndrome) [18–29].

In any case of suspected EA, the patient should undergo X-ray barium meal, 24-h esophageal pH monitoring, esophageal manometry, and esophagogastroduodenoscopy. The X-ray barium meal is often diagnostic and usually shows a dilated esophagus (megaesophagus) associated with a stricture of the distal esophagus ("mouse tail" or "bird beak" sign). The contrast material progresses in the stomach after a considerable time. The 24-h esophageal pH monitoring excludes the presence of a gastroesophageal reflux disease (GERD), which can produce dysphagia in up to 37 % of the patients. The esophagogastroduodenoscopy should demonstrate the absence of any stricture or mucosal abnormality. Esophagitis may be seen after aspiration of the retained fluid but is generally secondary to fermentation of the stagnant fluid. Finally, the diagnosis is reached with esophageal manometry that demonstrates the absence of normal esophageal motility (non-peristaltic waves) and of post-deglutitive LES relaxations.

EA is a progressive disease that does not resolve spontaneously. Therefore surgery is required as soon as a sure diagnosis is achieved, to prevent complications (failure to thrive, aspiration, etc.).

Preoperative Preparation

Three days before surgery, the patients are fed only with fluids in order to reduce aliment retention. The day before surgery, the patients are kept in fasting state. Enemas are administrated on the day before surgery to reduce colonic distension.

Anesthetic Consideration

Once in theater, premedication is performed with midazolam (0.5–0.75 mg/kg for a maximum of 15 mg). Then a nasogastric tube is introduced when the patient is still awake in order to clean the dilated esophagus and stomach and to reduce the risk of aspiration during tracheal intubation. A clean esophagus is mandatory to minimize spill of contents in the event of inadvertent perforation. A balanced general anesthesia is performed using thiopentone (5–7 mg/kg) and propofol (2.5–4.5 mg/kg) as inductors, fentanyl (2–4 μg/kg) or remifentanil (0.2–0.4 mg/kg/min) as analgesic, and atracurium (0.5 mg/kg) as muscle relaxant. After tracheal intubation, all the patients undergo mechanical ventilation (Drager Primus) with a mixture of O_2/air ($FiO_2 = 0.4$) and sevoflurane 0.8–1 MAC.

Electrocardioscopy, noninvasive blood pressure monitoring [mmHg], pulse oximetry (partial oxygen saturation [%] and pulse rate), and capnography (end-tidal CO_2 [mmHg]) are used to monitor cardiocirculatory and respiratory status during surgery and carbon dioxide insufflation. Airways respiratory rate [cycles/min] (AWRR), peak inspiratory pressure [cm H_2O] (PIP), and tidal volume [ml] (TV) are registered during ventilatory support, as well. No vesical catheter is required.

Operative Technique

The patient is placed supine in the lithotomy position with a reverse Trendelenburg. Skin preparation with meticulous scrubbing of the umbilicus is needed, and the operative field should include the whole abdomen from the pubis to the sternum and laterally to the anterior axillary lines in case conversion to open approach is required.

The surgeon stands between patient's legs. The assistant holding the telescope is on the right,

and the second surgeon is on the left of the patient. The monitor is positioned on the left of the patient at the head of the table.

CO_2 insufflation is used to create pneumoperitoneum up to 12 mmHg. Similarly as in all laparoscopic hiatal procedures, five cannulas are inserted in a semicircular pattern: (a) left paraumbilical (5 mm) for the retraction of the stomach during dissection, (b) umbilical (12 mm) for the telescope, (c) left subcostal (5 mm), and (d) right subcostal as working ports, and (e) epigastric/subxiphoid (5 mm) for retraction of the liver. Recently, we introduced the Step® technology for the stab insertion of the trocars.

The anterior gastric wall is grabbed to retract the esophagus downward. The parietal peritoneum is opened, and the anterior and lateral sides of the esophagus are freed to proceed cranially in the mediastinum (Fig. 65.1). A single longitudinal anterior myotomy and partial myectomy of the circular esophageal muscle, namely, modified Heller procedure, is performed using monopolar coagulation (scissors or hook or LigaSure™) (Fig. 65.2). The length of the myotomy is established by intraoperative manometry or by resorting to specific landmarks. Our landmarks of proximal and distal ends of the dissection are the proximal dilated esophagus where it is crossed by the anterior vagal nerve that moves from the left esophageal side to the anterior wall and the distal transverse esophageal vessel at the esophagogastric junction. Complete myotomy is demonstrated by mucosal herniation (Fig. 65.3). Mucosal integrity is checked by insufflating air inside the esophagus through the nasogastric tube. Mucosal herniation is protected using an anterior 180° gastric fundoplication, namely, Dor fundoplication. The anterior face of the stomach is fixed to the two muscular edges of the myotomy, to maintain it wide open, and to the right portion of the left crura using nonabsorbable synthetic sutures (Figs. 65.4 and 65.5).

Clear fluids and large-spectrum short-term antibiotic prophylaxis (piperacillin) are administrated intravenously during the first 24 h postoperatively, until feeding is started. The patients are fed on postoperative day 1 after a contrast X-ray

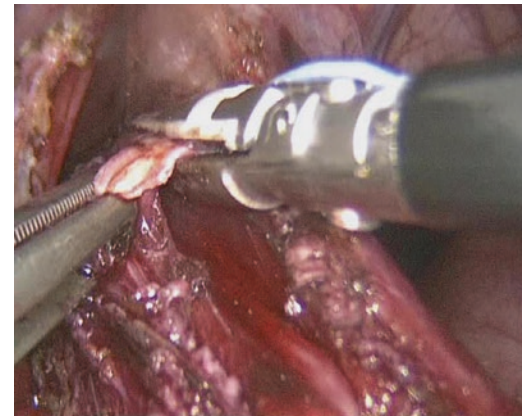

Fig. 65.2 Myotomy and partial myectomy of the circular esophageal muscle

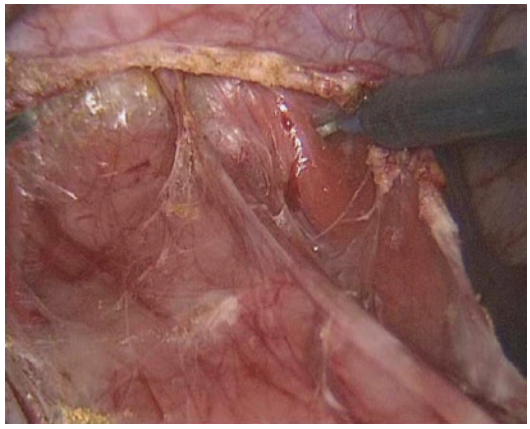

Fig. 65.1 Dissection of parietal peritoneum forward mediastinum space

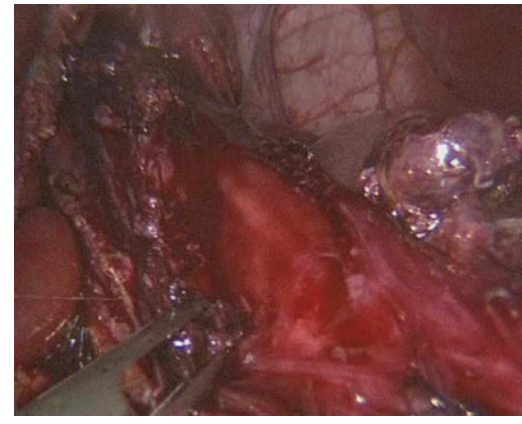

Fig. 65.3 Completed esophageal miotomy with evidence of mucosal herniation

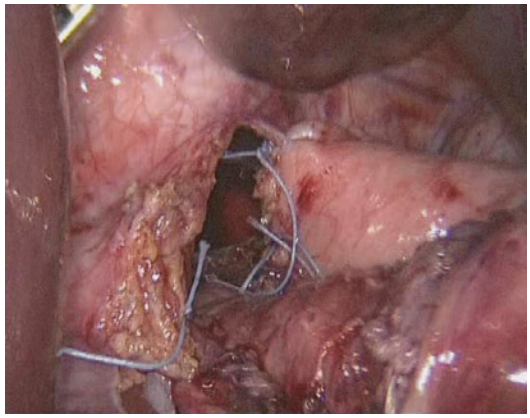

Fig. 65.4 Fixation of the anterior face of the stomach with the two muscular edges of the myotomy, and to the right portion of the left diaphragmatic crus

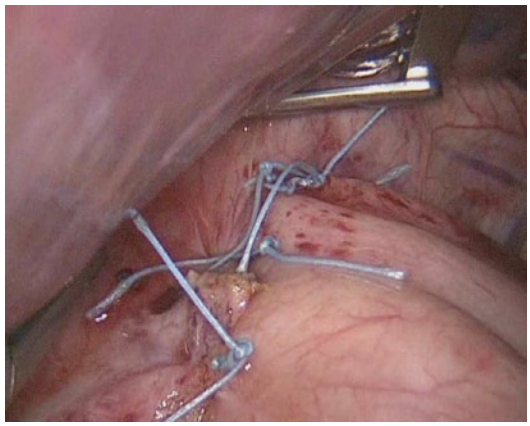

Fig. 65.5 Dor fundoplication at the end of the procedure

esophageal contrast meal (hydrosoluble contrast medium) performed in order to detect leakage or incomplete myotomy.

Results

Our series of patients (since January 1994) sums 20 children. Mean age at operation was 10 years (range 5–14) and mean weight was 45 kg (25–72). Six patients were female and 14 were male. All the procedures were accomplished laparoscopically. Mean operative time was 125 min (range 90–180).

In all patients we did not experience mucosal perforation. Bleeding from an esophageal vessel occurred in one case and clip positioning was thus required. No case needed transfusion nor reoperation.

Nasogastric tube was removed soon after awakening in 13/20 patients, on postoperative day 1 in 7/20. No case showed leakage during postoperative X-ray esophageal contrast meal. All patients were fed by the mouth on postoperative day 1 with fluid meals and were sent home with full oral feeding on postoperative day 3.

All the patients were afterward checked to detect intra- or early postoperative complications and followed to identify recurrence of symptoms due to stricture or appearance gastroesophageal reflux.

The Visick symptom score [30] was used to evaluate postoperative outcome: (1) no symptoms, (2) better than before surgery, (3) no modifications, and (4) new symptoms or complications.

Mean follow-up was 50 months (range 6–102). Postoperative clinical score was Visick 1 in 16 cases and Visick 2 in 4. In one of these three children, symptoms reappeared 6 months after surgery and completely disappeared after one esophageal dilation. One patient was neurologically impaired and required parental care for feeding. The other case experienced dysphagia with good esophageal viability and no recurrence of stricture as checked by X-ray esophageal barium meal and endoscopy. No case developed gastroesophageal reflux on pH monitoring.

Conclusions

The modified Heller myotomy and Dor fundoplication through a laparoscopic approach are, in our opinion, the gold standard to treat esophageal achalasia in the pediatric population.

Complications were low in this group of patients and comparable to other published reports in the literature [31–39].

Pearls

1. We suggest to dissect only the anterior esophageal wall and mediastinum in order to reduce the risk of GER.
2. It is mandatory to perform a high myotomy in the mediastinum (up to the dilated esophagus or to the previously described landmark) and low in the stomach (down to the transverse vessels previously described). Landmarks are of utmost importance in order to reduce recurrence.
3. The myotomy should be carried out with a hook diathermy pulling the muscle fibers far from the mucosa in order to avoid dangerous mucosal lesions or burns.
4. The anterior fundoplication is performed to reduce GER occurrence and to avoid leakage in case of mucosal perforation. It should always be performed in association with a modified Heller procedure.
5. Immediately before realimentation each patient should undergo a contrast study in order to exclude recurrence, residual disease, perforation, and GER.

Pitfalls

- Pneumatic dilatations of the esophagus should be avoided as these carry a high risk of complication and make it harder to perform a subsequent Heller-Dor procedure.
- Reflux is frequently present, but a 360° wrap should never be performed because of high risk of dysphagia.
- A long-term follow- up is strongly suggested because of complications such as esophagitis, stricture, and reflux.

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Esophageal Tumors in Childhood and Adolescence: Benign and Malignant

66

Till-Martin Theilen and Michael La Quaglia

Introduction

Of all tumors diagnosed during childhood and adolescence, less than 5 % occur in the gastrointestinal (GI) tract [1–3]. Of these GI neoplasms, only a very small percentage is comprised of esophageal tumors. In this chapter, we will review all published case reports of patients 21 years of age and younger with esophageal tumors, including both benign and malignant entities. Based on the number of reported cases, benign tumors are more common than malignant ones. Of 136 pediatric cases, 94 (70 %) describe benign tumors, and 42 (30 %) describe malignant tumors (Table 66.1). Leiomyoma/leiomyomatosis is the most common benign esophageal tumor, as well as the most common pediatric esophageal tumor overall, and comprises 39 % of all reported cases (Fig. 66.1). Squamous cell carcinoma (SCC) and adenocarcinoma (AC) are the most commonly reported malignant esophageal tumors (see Fig. 66.1).

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The incidence data are only available for malignant esophageal tumors. Table 66.2 shows the consolidated incidence for pediatric esophageal cancers registered in some of the largest cancer registries in the world [3–6]. Overall, the incidence of esophageal cancer in infants and children is extremely low. In the United States, for example, only nine cases of esophageal cancer in patients under the age of 20 were registered in the Surveillance, Epidemiology, and End Results database between 1973 and 2007 [3]. Some registries provide the total number of esophageal tumors among all age groups and the total number of all pediatric cancers. In instances in which data are available, we calculated the relationship between the number of reported cases and the total number of esophageal tumors among all age groups or the total number of childhood malignancies. Worldwide, we found that 0.004–0.1 % of all esophageal cancers occur in patients under the age of 21. Similarly, of all pediatric cancers, 0.02–0.2 % are esophageal cancers (see Table 66.2). Interestingly, geographical regions with an increased incidence of adulthood esophageal cancer (e.g., some areas of India) do not likewise have an increased incidence of childhood esophageal cancer [7].

A comparison of the age of onset among children with esophageal cancer reveals that benign esophageal tumors have an earlier onset (median patient age at diagnosis of 11 years [range, 0.2–21 years]) than malignant esophageal

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Table 66.1 Cases of esophageal tumors diagnosed in pediatric patients aged 21 years and younger reported in the world literature

Neoplasm	# of cases reported	Median age at diagnosis (range)	Male: female ratio
Benign			
Leiomyoma/leiomyomatosis	53	11 year (1.6–20)	1:3.4
Hyperplastic polyps	12	11 year (9–17)	6:1
Squamous papilloma/papillomatosis	6	3.5 years (1.4–14)	1:1
Hemangioma and lymphangioma	5	6 months (3–19)	1:1.5
Neurofibroma	3	14, 19, 19 years	3 F
Hamartoma (not otherwise classified)	3	2, 3, 6 years	1:2
Aggressive fibromatosis	2	4, 9 years	1:1
Lipoma	2	4, 6 years	1:1
Inflammatory pseudotumor	2	14, 15 years	1:1
Rhabdomyoma	2	8, 21 year	1:1
Granular cell tumor	2	14, 19 years	2 F
Plexiform schwannoma	1	11 year	1 F
Undifferentiated mesenchymal neoplasm	1	15 years	1 M
Total	*94*	*11 year (0.2–21)*	*1:1.5*
Malignant			
Squamous cell carcinoma	20	15 years (8–21)	1.2:1
Adenocarcinoma	17	16 years (8–20)	5:1
Synovial sarcoma	3	14, 15, 20 year	2:1
Lymphosarcoma	1	4 years	1 M
Melanoma	1	7 years	1 M
Total	*42*	*15 years (4–21)*	*2.2:1*
Overall	136	13 years (0.2–21)	1:1.1

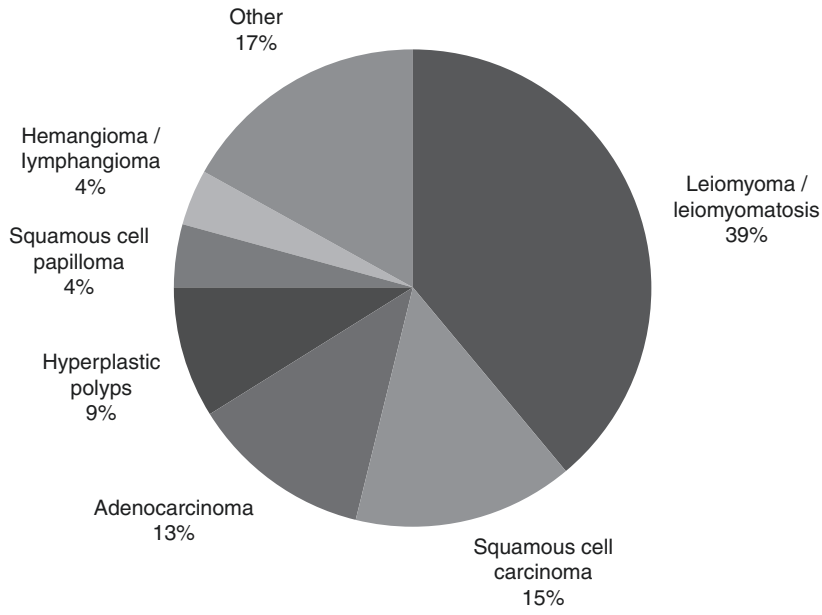

Fig. 66.1 Esophageal tumors diagnosed in pediatric patients aged 21 years and younger based on the total number of cases reported in the world literature. "Other" includes synovial sarcoma, neurofibroma, hamartoma, inflammatory pseudotumor, fibromatosis, rhabdomyoma, lipoma, granular cell tumor, plexiform schwannoma, undifferentiated mesenchymal tumor, melanoma, and lymphosarcoma

Table 66.2 Consolidated incidence data for pediatric esophageal cancers worldwide

Registry	Country/world region	Study period	Number of cases	Esophageal cancer		Childhood cancer	
				Absolute number (all ages)	Percentage of patients under 21 years	Absolute number	Percentage of esophageal cancer
AACR (AIHW)	Australasia	1982–2005	4	21,623	0.02	–	–
NCRP (ICMR)[a]	India	1984–1993	18	22,732	0.08	19,182	0.09
		1994–2003	11	19,673	0.06	–	–
NCRP (ICMR)[b]	India	1982–1987	6	4,496	0.1	3,184	0.2
		1990–2004	17	18,164	0.09	17,996	0.09
CRECJ (JES)[c]	Japan	1988–1999	12	–	–	–	–
NCR	Netherlands	1989–2007	1	22,216	0.005	–	–
NORDCAN (ANCR)	Scandinavia	1943–2008	2	14,532	0.01	–	–
ONS	UK[d]	1992–2008	5	102,324	0.004	–	–
SEER (NCI)	USA	1973–2007	9	–	–	–	–
NCRP (CDC)	USA	1999–2005	11	69,106	0.02	49,442	0.02
UICC (WHO)	5 continents	1983–1997	47	224,613	0.02	–	–

Data adapted from: *AACR* Australasian Association of Cancer Registries, *AIHW* Australian Institute of Health and Welfare, *NCRP* National Cancer Registry Program, *ICMR* Indian Council of Medical Research, *CRECJ* Comprehensive Registry of Esophageal Cancer in Japan, *JES* Japan Esophageal Society, *NCR* Netherlands Cancer Registry, *ANCR*, reported cases from Denmark only, NORDCAN Association of Nordic Cancer Registries, *ONS* Office for National Statistics, *NCRP* National Cancer Registry Program, *CDC* Centers for Disease Control and Prevention, *SEER* Surveillance, Epidemiology, and End Results Program, *NCI* National Cancer Institute, *UICC* International Union Against Cancer, *WHO* World Health Organization

[a]Hospital-based registry

[b]Population-based registry

[c]Age limit <29 years

[d]England only

tumors (median patient age at diagnosis of 15 years [range, 4–21 years]) (see Table 66.1). Of patients aged 21 years and younger with malignant esophageal tumors, only four patients were younger than 10 years [8–11]. However, of all pediatric patients with benign esophageal tumors, 50 % were diagnosed before the age of 10. A comparison of the gender distribution among pediatric esophageal cancers reveals that benign tumors are almost evenly distributed among boys and girls (M:F = 1:1.5), whereas malignant tumors are more common in boys (M:F = 2.2:1) (see Table 66.1).

Although most pediatric esophageal tumors are benign and thus are associated with an excellent outcome, they may still adversely affect a child's health. An expanding benign esophageal lesion can lead to life-threatening conditions if it compresses the airway or hinders nutritional intake. With effective treatment, mortality from benign tumors only occurs as a result of operative complications or underdiagnosis and is found

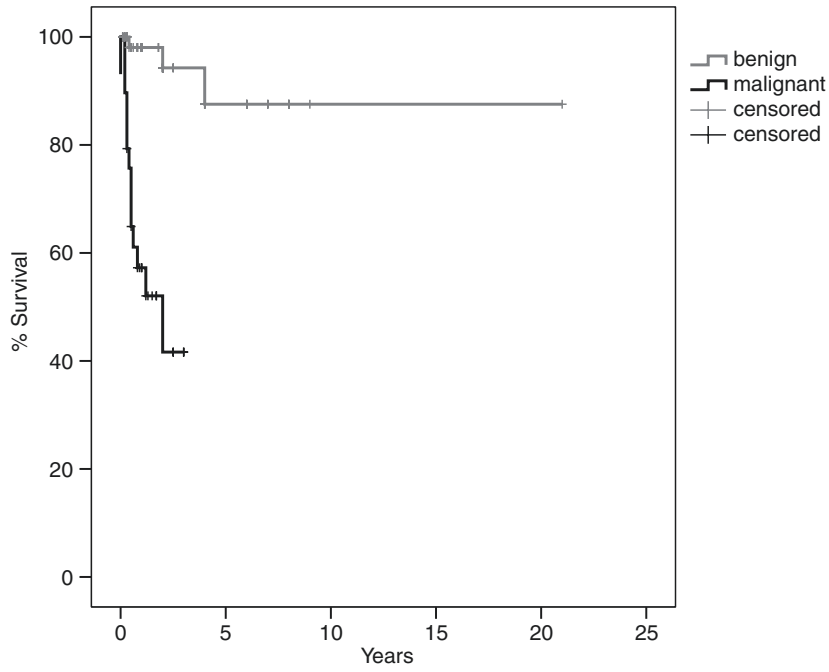

Fig. 66.2 Kaplan-Meier survival curves for pediatric patients aged 21 years and younger with benign ($N=70$) and malignant ($N=29$) esophageal tumors. Survival was significantly worse for patients with malignant tumors than for those with benign tumors ($P<0.0001$, log-rank test)

only historically [12]. On the other hand, the outcome of malignant esophageal tumors in children and adolescents is devastatingly poor. Of the 42 reported cases of malignant esophageal tumors, 36 mentioned follow-up status, and the median survival time was 2 years. Of the 94 reported cases of benign esophageal tumors, 70 mentioned follow-up data. The overall survival of pediatric patients with malignant tumors was significantly worse than that of those with benign tumors ($P<0.0001$, log-rank test). Figure 66.2 shows the Kaplan-Meier survival curves for both patient groups.

Clinical Presentation

A growing mass in the esophagus may lead to three symptom-causing conditions: obstruction of the esophageal lumen, compression of surrounding structures, and tumor ulceration with bleeding.

We reviewed all 136 case reports for presenting symptoms. As shown in Table 66.3, dysphagia is the most common presenting symptom for both benign and malignant esophageal tumors. However, with the exception of dysphagia, the clinical presentation of benign and malignant entities differs remarkably. In children with large and slow-growing benign tumors, respiratory symptoms (e.g., wheezing/dyspnea, recurrent pneumonia/bronchitis) due to airway compression and micro-aspirations are the most common presenting symptoms after dysphagia. In fact, some of the patients described in the literature with these symptoms were treated for asthma or recurrent pneumonia for years before additional evaluation revealed that an esophageal tumor was the underlying cause of their respiratory complaints [13–17]. On the other hand, in pediatric patients with malignant tumors, signs of physical deterioration are predominant in the clinical picture with weight loss, anemia, and dehydration being the most common presenting symptoms after dysphagia.

Unlike most malignant esophageal tumors, benign esophageal tumors do not immediately cause severe symptoms. In fact, many benign tumors are only found incidentally at autopsy. Benign tumors generally become symptomatic when they grow large enough to cause physical symptoms including dysphagia, respiratory

Table 66.3 Presenting symptoms of pediatric patients diagnosed with esophageal tumors

Benign (N=94)	N (%)	N (%)	Malignant (N=42)
Dysphagia	50 (53.2)	36 (85.7)	Dysphagia
Epigastric/retrosternal pain	26 (27.7)	23 (54.8)	Weight loss
Wheezing/dyspnea	25 (26.6)	15 (35.7)	Anemia
Recurrent pneumonia/bronchitis	22 (23.4)	9 (21.4)	Dehydration
Vomiting	22 (23.4)	8 (19.0)	Nausea
Weight loss	14 (14.9)	6 (14.3)	Vomiting
Coughing	12 (12.8)	4 (9.5)	Epigastric/retrosternal pain
Regurgitation	11 (11.7)	2 (4.8)	Recurrent pneumonia/bronchitis
Growth retardation	8 (8.5)	2 (4.8)	Hematemesis
Stridor	6 (6.4)	2 (4.8)	Wheezing/dyspnea
Hematemesis	5 (5.3)	1 (2.4)	Odynophagia
Anemia	5 (5.3)	1 (2.4)	Constipation
Constipation	4 (4.3)	1 (2.4)	Melena
Dysphonia/hoarseness	3 (3.2)	0 (0)	Regurgitation
Intermittent cyanosis	3 (3.2)	0 (0)	Growth retardation
Melena	3 (3.2)	0 (0)	Stridor
Nausea	3 (3.2)	0 (0)	Dysphonia/hoarseness
Intermittent brady-/tachycardia	2 (2.1)	0 (0)	Intermittent cyanosis
Drooling	1 (1.1)	0 (0)	Intermittent brady-/tachycardia
Prominent jugular veins	1 (1.1)	0 (0)	Drooling
Dehydration	0 (0)	0 (0)	Prominent jugular veins
Odynophagia	0 (0)	0 (0)	Coughing

compromise, or discomfort and pain. Patients are typically able to alleviate these symptoms, sometimes for years [18]. Of the 94 case reports of benign tumors, 44 reported the time to presentation after first symptoms. In these patients, the mean time between the first onset of symptoms and presentation was 3.5 years. Malignant tumors, however, become clinically apparent relatively quickly. Of the 42 case reports of malignant tumors, 24 reported the time to presentation after first onset of symptoms. These patients presented at an average of 3 months (±2.6 months) after the onset of symptoms.

When a pediatric patient presents with dysphagia, the differential diagnosis of esophageal tumors should include the following: achalasia (cardiospasm), esophageal webs, esophageal (duplication) cysts, esophageal stricture due to causes other than cancer, extra-esophageal lesions compressing the esophageal tube (such as mediastinal lymphomas), and esophageal impairment due to neurologic causes.

Diagnostic Studies

Contrast studies and endoscopy are usually the initial diagnostic interventions for suspected esophageal lesions. But an experienced and skilled diagnostician is needed as intramural tumors can easily be overlooked on these studies [19]. Although biopsies play an important role in the diagnosis-making process, they are frequently nondiagnostic in tumors covered by an intact mucosa, such as leiomyomas. Thus, biopsies of intact-appearing mucosa are not generally recommended by some investigators [18, 20].

We reviewed the 94 case reports of benign esophageal tumors for any false primary diagnosis. We found that 11 patients (11.7 %) were initially diagnosed with and treated for achalasia [18, 21–27] and that five patients (5.3 %) were initially diagnosed with and treated for asthma [13–17]. Benign tumors—most frequently leiomyoma/leiomyomatosis—were eventually found to be the underlying cause of these patients' symptoms. When distinguishing esophageal

leiomyoma/leiomyomatosis from achalasia, diagnosticians should consider the length of the constricted part on the contrast studies. Most often, the constricted part is much longer in patients with achalasia when compared to leiomyoma [28–30].

Additional diagnostic studies for esophageal tumors include endoscopic ultrasonography; computed tomography of the chest, abdomen, and pelvis; and positron emission tomography to delineate the extent of local and metastatic disease. These imaging modalities are also used to stage malignant esophageal tumors, which are classified according to the American Joint Committee on Cancer TNM staging system [31].

Etiology

The pathophysiology of esophageal tumors in pediatric patients is not completely understood. In general, the pathophysiology underlying esophageal tumors in adults is thought to be the same in children and adolescents. In fact, there is no known risk factor or genetic defect for any esophageal tumor in children.

The intimate relationship between the trachea, bronchi, and esophagus during embryologic development may lead to the formation of ectopic tracheal or bronchial tissue within the esophagus. This displaced tissue can be the origin of hamartomatous lesions within the esophageal lumen [32]. Also, the presence of ectopic gastric cells within the esophagus has long been thought to be the origin of AC [33].

An accumulation of familial traits has been observed in cases of leiomyomatosis associated with Alport syndrome (nephropathy, cataracts, hearing impairment) [34]. In these cases, a mutation in the type IV collagen gene is inherited. A familial trait has also been reported in cases of AC and SCC in adults but has not been reported in children with AC and SCC [35].

Esophageal tumors also arise in areas of chronic inflammation due to gastroesophageal reflux (GER) or caustic injury. Although the latency period between the onset of chronic inflammation and the development of Barrett's esophagus (BE) and subsequently AC during childhood seems to be too short, a few cases of synchronous BE and AC have been reported in children [36]. The same is true for chronic inflammation leading to dysplasia and SCC after caustic injury [37]. Importantly, chronic irritation may lead to the formation of not only malignant tumors but also benign tumors such as hyperplastic polyps.

Of special interest are cases of leiomyoma, esophageal AC, and esophageal SCC developing decades after the repair of esophageal atresia and tracheoesophageal fistula repair [38–43]. In patients who have undergone repair of esophageal atresia as an infant, the esophageal anatomy is altered. Impairment of the lower esophageal sphincter leads to GER-related problems such as heart burn, esophagitis, and even BE and cancer [44]. Lifelong follow-up is recommended for these patients as they transition from pediatric to adult gastroenterology care.

Treatment

The management of pediatric esophageal tumors is based on the same principles used in adults. For malignant tumors, complete resection with radical lymphadenectomy is the gold standard of therapy. Depending on the location of the primary tumor, lymph nodes need to be evaluated along typical drainage pathways. Tumors in the lower third of the esophagus and in the gastroesophageal junction have a high prevalence of positive lymph nodes around the celiac trunk and the lesser gastric curvature [45]. Tumors in the upper two-thirds of the esophagus primarily drain via lymphatics along the aorta and vena cava, along the esophagus itself, and in the supraclavicular region and neck. In adults, the primary esophageal tumor should be resected with proximal and distal margins of up to 7–10 cm [46]. However, the application of these margins in small children can be very challenging.

For malignant esophageal tumors, the tumor and lymph node resection can be achieved using either a transhiatal, transthoracic, or cervical approach or a combination. The transthoracic

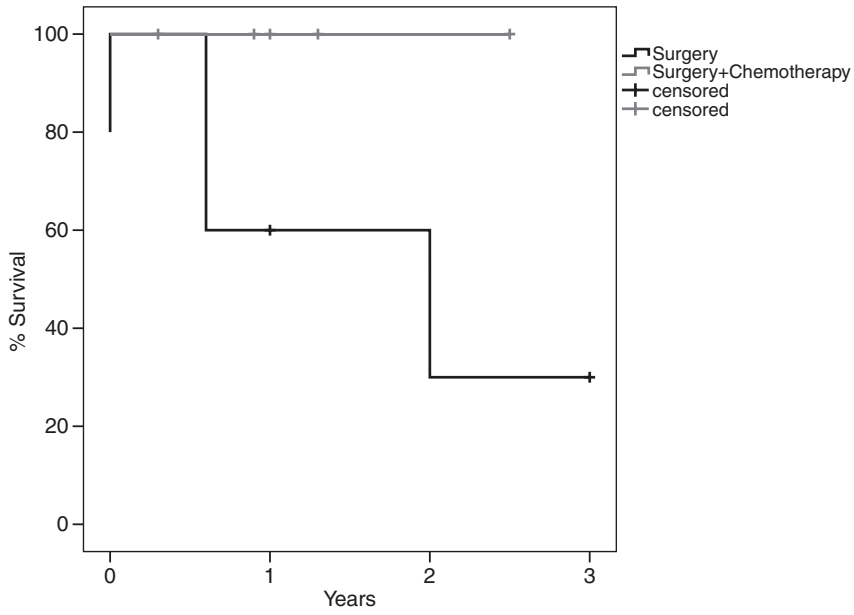

Fig. 66.3 Kaplan-Meier survival curves for pediatric patients aged 21 years and younger with esophageal adenocarcinoma treated with surgery plus chemotherapy versus those treated with surgery alone ($N=5$). There was no significant difference in survival between these two groups ($P=0.1573$, log-rank test)

approach (Ivor Lewis technique) allows greater exposure of the operative field and thus allows more extensive resection of the thoracic lymphatics. However, compared to the transhiatal technique, the transthoracic technique has been associated with increased operative morbidity in adults [47]. However, in terms of overall survival in adults, there are no significant differences between these two approaches [47]. The cervical approach is applied for tumors in the upper esophagus without needing a gastroesophageal anastomosis. Minimally invasive techniques for the resection of malignant tumors are being used with increasing frequency; however, long-term follow-up is still needed to adequately evaluate the outcomes [48].

Complete resection with radical lymphadenectomy is the primary treatment and the only chance for cure. In adults, there is emerging evidence that multimodality therapy in combination with operative resection results in superior survival rates over surgery alone [47]. In the pediatric population, however, it is almost impossible to assess the effectiveness of different treatment strategies because of the low number of cases. Of the pediatric patients with malignant esophageal tumors listed in Table 66.1, five patients with AC received a combination of operation and chemotherapy, and five patients underwent operation alone [36, 38, 49–55]. Both patient groups had comparable extent of disease with local lymph node metastases at presentation (two patients in the surgery plus chemotherapy group vs. three patients in the surgery alone group). There was a trend toward improved survival for the combination therapy group; however, this difference in survival did not reach statistical significance (Fig. 66.3). Studies with larger patient populations will be needed to generate more reliable data on the treatment outcomes of pediatric patients with malignant esophageal tumors.

For patients with unresectable disease, palliative treatment to relieve progressive dysphagia is the only treatment option. Stent placement is usually the procedure of choice. Other palliative treatment options for dysphagia include repeated endoscopic dilatations, intraluminal laser therapy, and single-dose external beam radiation therapy.

Benign esophageal tumors are treated less aggressively than their malignant counterparts. Nodular intramural tumors can usually be enucleated completely without resecting portions of the esophagus. Well-circumscribed intraluminal polypoid tumors can generally be resected endoscopically. However, when tumor ulceration has

occurred or when the tumor encloses the esophagus circumferentially, esophageal resection will be necessary.

After esophageal resection, the colon, jejunum, or stomach can be used to reestablish enteric continuity. Colonic interposition is preferred by many pediatric surgeons as an esophagogastric anastomosis can lead to severe reflux in the remaining esophagus later in life.

After esophagectomy and partial gastric reconstruction, gastric emptying may be impaired. Pyloroplasty or pyloromyotomy may improve gastric outlet obstruction in these patients. However, in adult esophageal cancer patients, these adjunct procedures have been shown to provide only short-term, but not long-term, relief of gastric outlet obstruction [56].

The most worrisome complication is insufficiency of the enteric-esophageal anastomosis. Infarction of the interposed organ due to chronic venous obstruction can also occur weeks to months after the operation. Other complications include esophageal stenosis, gastric reflux with peptic ulcerations in the esophageal stump, and comprised pulmonary function.

Benign Esophageal Tumors

Although benign esophageal tumors can arise from all parts of the wall of the esophagus, the vast majority are leiomyomas that arise from the muscle layers of the esophagus. Other benign esophageal tumors that have been described in the pediatric population are listed in Table 66.1.

Leiomyoma/Leiomyomatosis

Leiomyomatous lesions are the most common esophageal tumors in the children (see Table 66.1). They typically present either as a localized, well-circumscribed nodule (leiomyoma), a diffuse thickening of the entire esophageal muscle wall (leiomyomatosis), or a combination [57]. In 1989, Bourque and colleagues published one of the largest reviews of esophageal leiomyomas in children, which included a total of 22 case reports [18]. To date, 53 cases of childhood leiomyomatous lesions have been reported in the literature [22, 26, 34, 58–85]. A review of these 53 cases shows that the median patient age at diagnosis is 11 years (range, 1.6–20 years) and that these tumors are more common in girls than boys (M:F = 1:3.4).

Leiomyomatous lesions most frequently arise from the inner, circular layer of the muscularis propria. The muscularis mucosa and the longitudinal layer of the muscularis propria are rarely involved [86, 87]. In children and adolescents, these lesions usually present as diffuse leiomyomatosis, often with extension in a circumferential direction, which leads to progressive narrowing of the esophageal lumen [18, 88]. In contrast, in adults, these lesions typically present as a single leiomyoma with a non-circumferential growth pattern [46]. Importantly, the distal esophageal encasement caused by a leiomyoma can lead to misdiagnosis. As mentioned above, some pediatric patients with leiomyoma/leiomyomatosis were initially diagnosed with and treated for achalasia, because both conditions have similar clinical features.

Leiomyomas can grow to be quite large, weighing more than 1,000 g [24, 83]. In the 53 reported cases of childhood leiomyoma/leiomyomatosis, approximately 50 % of the lesions occurred in the distal third of the esophagus, and the remaining 50 % occurred throughout the entire esophagus. Extension beyond the gastroesophageal junction into the proximal stomach occurred in about half the cases.

Histologically, there is no difference between childhood and adult leiomyomas. Leiomyomas are positive for alpha-smooth muscle actin and desmin and are negative for GI stromal tumor (GIST) markers CD34 and CD117 (c-Kit) and neuronal tumor marker S-100 [89–91].

Familial etiologic factors are found in about 30 % of all reported cases of pediatric leiomyoma/leiomyomatosis [15, 22, 28, 61, 64, 69, 70, 72, 77, 79, 84]. The association between leiomyomatosis and Alport syndrome is due to simultaneous mutations in the type IV collagen genes *COL4A5* and *COL4A* [61, 72, 92, 93].

The coexistence of esophageal and vulvar leiomyomatous lesions, defined as esophagovulvar

syndrome, has been described in some patients [94, 95]. Also, in some patients with leiomyomatous lesions, additional foci of disease have been found in the small intestine or rectum, viscera, and tracheobronchial system [58, 96, 97]. Therefore, when evaluating a child who presents with leiomyoma/leiomyomatosis, clinicians should take a complete family history for Alport syndrome and perform a careful examination of the esophagus, lung, rectum, perineum, and genitalia to exclude generalized disease.

The management of leiomyoma/leiomyomatosis includes enucleation (for nodular tumors), subtotal or total esophagectomy (for large tumors or those with a diffuse growth pattern), and replacement procedures. Partial proximal gastrectomy is necessary when the stomach is involved. Myotomy, as performed for achalasia, has been shown to be ineffective for treatment of esophageal leiomyomas [18].

After complete resection, the prognosis of pediatric patients is excellent. In patients with leiomyomatous lesions associated with Alport syndrome, the severity of nephropathy determines the course of disease.

Hyperplastic Polyp

Twelve cases of esophageal hyperplastic polyps in pediatric patients have been reported [98–107]. A review of these 12 reported cases shows that the median patient age at diagnosis is 11 years (range, 9–17 years) and that these polyps are much more common in boys (M:F = 6:1). In six cases, a single polyp was located in the gastroesophageal junction; in five cases, the polyp was located in the distal third of the esophagus; and in one case, the location of the polyp was not specified.

Hyperplastic polyps most commonly consist of hyperplastic gastric foveolar-type mucosa with varying amounts of esophageal squamous epithelium. If stromal inflammation and granulation tissue predominates, hyperplastic polyps are designated as "inflammatory polyps."

The pathophysiology of hyperplastic polyps is poorly understood, but it is speculated that esophagitis caused by GER is the precursor for polyp formation. Seven of the 12 pediatric patients had GER and presented with retrosternal pain and histologic signs of esophagitis [100, 101, 103, 104, 106, 107].

Of the 12 cases of hyperplastic esophageal polyps, 3 were described in children with neurofibromatosis type 1 [100, 102]. A true association between these two conditions, however, has not been established [102].

Malignant transformation of a hyperplastic polyp has not been reported. However, areas of epithelial dysplasia have been seen next to hyperplastic polyps. It is probable that the same mechanism of chronic GER leads to the development of these simultaneous lesions [108].

Endoscopic polypectomy is the preferred treatment for hyperplastic polyps. However, eliminating GER might also be an effective therapy. For example, a pediatric patient with an esophageal inflammatory polyp and ulcerative colitis was treated with medication for reflux esophagitis, which resulted in the marked regression of the polyp [104]. In another child, the esophageal inflammatory polyp resolved 9 months following antireflux surgery [107].

Squamous Cell Papilloma

Six cases of esophageal squamous cell papilloma in pediatric patients have been described [109–114]. A review of these 6 reported cases shows that the median patient age at diagnosis is 3.5 years (range, 1.4–14 years) and that these papillomas are evenly distributed among boys and girls (M:F = 1:1). Unlike in adults, in whom squamous cell papillomas tend to be pedunculated, occur in single numbers, and are found mostly on the posterior wall of the lower esophagus [113], in children and adolescents, squamous cell papillomas tend to be sessile, to occur in multiple numbers, and to be found within the entire esophagus [114, 115].

Two of the six pediatric patients with esophageal squamous cell papilloma had simultaneous laryngeal papilloma; in these two patients, the larynx was the site of initial manifestation of disease [110, 114]. Therefore, endoscopic inspection of

the esophagus should be performed in pediatric patients diagnosed with laryngeal squamous cell papilloma and vice versa.

Etiologic factors for esophageal squamous cell papilloma are thought to be any irritation of the esophageal mucosa such as that caused by chronic acid reflux, irradiation, and ingestion of corrosive chemicals or foreign bodies [114]. Malignant transformation of a squamous cell papilloma has not yet been reported in children.

Resection of asymptomatic multiple squamous papillomata is generally not recommended, partly because recurrences are common, and because multiple resections increase the risk of developing esophageal stenosis. Also, endoscopic resection of esophageal squamous cell papilloma in children is frequently not possible because of the high number of lesions. Total spontaneous regression of papillomatosis of the entire esophagus has been described in a patient 2 years after removal of a laryngeal tumor [111].

Hemangioma and Lymphangioma

Hemangioma and lymphangioma are two types of vascular tumors commonly found in children. However, they usually do not occur in the esophagus. Three cases of esophageal hemangioma and two cases of mixed hemangioma/lymphangioma in pediatric patients have been reported [116–118]. In these cases, the tumors occurred during the first months of life (median patient age at diagnosis of 6 months [range, 3–19 months]), and they tended to occur in the proximal part of the esophagus. In two cases, the tumors grew larger than 10 cm. In one case, a bulky pedunculated hemolymphangioma of the esophagus grew so large that it refluxed into the oral cavity, leading to respiratory distress [116].

Spontaneous involution of hemangiomas and lymphangiomas in infants and young children is common. However, when esophageal hemangiomas and lymphangiomas become symptomatic, their removal is warranted. Treatment with steroids has not been effective [118].

Schwannoma and Neurofibroma

Schwannomas and neurofibromas are slow-growing spindle cell tumors that are positive for S-100 protein and neuron-specific enolase (NSE) because of their derivation from cells of the neural crest. Plexiform variants of these tumors arise from nerve bundles and tend to grow large and extend through tissue layers. They most commonly occur on the skin and very rarely involve the GI tract. Thus, esophageal manifestation of these tumors is very rare.

Only one case of esophageal plexiform schwannoma in a pediatric patient has been described [119]. In this case, a plexiform schwannoma in the esophagotracheal space and invading the esophagus was found in an 11-year-old girl with neurofibromatosis type 2 [119]. A frequent association between neurofibromatosis type 2 and plexiform schwannoma has been reported [120].

Three cases of esophageal neurofibroma in pediatric patients have been reported [121–123]. All three patients were adolescent females presenting with tumors in the distal and middle third of the esophagus. However, it is not clear whether all these tumors truly originated from the esophageal wall or primarily occurred in the posterior mediastinum and invaded the esophagus [123].

Unlike plexiform schwannomas, which are not associated with malignancy, plexiform neurofibromas carry a 10 % risk of malignant transformation [124]. For proper histologic evaluation, complete resection is required for both tumor types [124]. However, resection is often complicated because of the invasive nature of these tumors.

Hamartoma

The intimate relationship between the trachea and esophagus during embryonic development may explain the rare presence of cartilage and epithelia of the respiratory tract within the esophageal wall. Here, these sequestered cells can form

hamartomatous lesions with varying amounts of cartilage, respiratory epithelium, mucus glands, adipose, and fibrous tissue. Three cases of esophageal hamartoma in pediatric patients (aged 2, 3, and 6 years) have been described [32, 125, 126]. In two cases, the tumor was located in the proximal esophageal muscle wall; in the third case, the tumor was located in the distal esophagus as a pedunculated polyp. All three tumors had cartilaginous tissue and varying amounts of respiratory, gastric, fat, muscle, and fibrous tissue, as well as bronchial-like glandular tissue. In all three cases, resection was curative.

Aggressive Fibromatosis (Desmoid Tumor)

Two cases of aggressive fibromatosis (desmoid tumor) of the esophagus in pediatric patients have been found [25, 127]. In one patient, the tumor arose directly from the esophagus and upper stomach [25]. In the other case, the tumor originated in the prevertebral fascia and invaded the esophageal wall [127]. Aggressive fibromatosis of the abdomen usually occurs in the abdominal wall, mesentery, or retroperitoneum [127]. The differential diagnosis of aggressive fibromatosis includes GIST. One group recently described an esophageal tumor in a 15-year-old boy that had histologic features resembling those of GIST [128]. Histochemical analysis, however, failed to confirm this diagnosis, leading to the descriptive diagnosis of an undifferentiated mesenchymal tumor (see Table 66.1).

Management of locally aggressive desmoid tumors includes radical excision and optional adjuvant radiation therapy. Complete local excision is often limited because of the invasiveness of these tumors, especially if vital structures are involved. Since spontaneous regressions have also been reported [25, 127], it remains unclear if radical and often mutilating dissection is indicated in every case. These tumors have a high rate of recurrence, especially in cases with positive resection margins.

Lipoma

Manifestations of lipoma in the GI tract mainly occur in the stomach and the small and large intestines. Thus, esophageal manifestations are extremely rare, but they can be life threatening in the case of pedunculated tumors. Long pedicles can regurgitate into the pharynx, where they confer the risk of suffocation [129].

Only two cases of esophageal lipomas in pediatric patients have been reported in the world literature [17, 130]. One patient was treated for asthma for 2 years before being diagnosed with an esophageal lipoma at age 6. This patient had an intraluminal pedunculated tumor in the proximal esophagus, which was removed by open esophagotomy [17]. The other patient presented with an intramural lipoma in the proximal two-thirds of the esophagus at the age of 4. The tumor had displaced the trachea, resulting in respiratory compromise [130].

Endoscopic resection, when feasible, is the preferred treatment for pedunculated lipomas; otherwise, an open approach is needed.

Inflammatory Pseudotumor

The term "inflammatory pseudotumor" (IPT) is used to describe a spectrum of tumors associated with a previous infection or tissue injury. Before the term IPT was established, these tumors were referred to as "plasma cell granulomas," "post-inflammatory tumors," or "xanthomatous pseudotumors." Importantly, an association between IPTs and malignant neoplasms has been reported [131].

IPTs primarily affect young adults, and they occur mainly in the lungs and less commonly in the stomach and liver [132]. Only two cases of esophageal IPT in pediatric patients have been described [133, 134]. In the first case, an IPT occurred in a 15-year-old boy 9 years after he underwent treatment for Wilms' tumor. The IPT involved the gastroesophageal junction, parts of the stomach, and the liver [134]. In the second case, an IPT occurred in a 14-year-old girl who

presented with a tumor at the gastroesophageal junction that involved the stomach, pancreas tail, and splenic hilum [133].

Because esophageal IPTs can mimic malignant esophageal neoplasms, it is important to perform a thorough histologic evaluation to exclude malignancy [135]. Histologically, IPTs are characterized by an inflammatory infiltrate consisting of varying amounts of plasma cells, lymphocytes, and macrophages within a fibrous tumor.

The IPT that occurred in the 14-year-old girl was interpreted as being an "inflammatory myofibroblastic tumor" [133]. Among IPTs, inflammatory myofibroblastic tumors have received special attention because they have been shown to behave like malignant neoplasms in different anatomic sites. Chromosomal aberrations, namely, the activation of anaplastic lymphoma kinase and p53, have been found in some inflammatory myofibroblastic tumors [136].

Complete resection is the primary treatment for IPTs. Other treatment options, including corticosteroid therapy, anti-TNF-alpha antibody therapy, nonsteroidal anti-inflammatory drugs, and chemotherapy, are currently being investigated in clinical trials [133, 136].

Rhabdomyoma

Cardiac rhabdomyomas are classified as hamartomatous lesions, while extracardiac rhabdomyomas are classified as true neoplasms. Of all extracardiac rhabdomyomas, 93 % occur in the head and neck region—most frequently the larynx and pharynx—in adult male patients [137]. There are three subtypes of extracardiac rhabdomyomas: fetal, adult, and genital. Two cases of adult-type rhabdomyoma of the esophagus in young patients have been reported [16, 138]. In the first case, a rhabdomyoma occurred in an 8-year-old boy; [16] in the second case, a rhabdomyoma occurred in a 21-year-old woman [138]. These tumors were located in the proximal and middle third of the esophagus.

Resection is the treatment of choice for esophageal rhabdomyoma. Local recurrences have been reported and are mostly due to incomplete resection of a multicentric lobulated tumor [16].

Granular Cell Tumor

Granular cell tumor (Abrikossoff's tumor) most commonly presents in the skin. Only two cases of an esophageal granular cell tumor in pediatric patients have been described: one in a 14-year-old girl [139] and another in a 19-year-old girl [140].

The pathophysiology of granular cell tumors remains poorly understood. Both patients presented with progressively worsening dysphagia and GER symptoms. In both patients, the tumors occurred in the distal third of the esophagus. These tumors' ultrastructure and their positivity for NSE and S-100 protein support the hypothesis that they originate from Schwann cells or are derived, to some extent, from neural tissue [113, 139].

In adults, a 2–4 % malignant transformation rate has been reported for these tumors [141]. Therefore, excision seems warranted. However, it has also been suggested that these tumors should be excised only if they are growing rapidly and become symptomatic [139].

Malignant Esophageal Tumors

The vast majority of malignant esophageal tumors diagnosed in patients aged 21 and younger are SCC and AC. Other malignant esophageal tumors reported in the literature include synovial sarcoma, spindle cell sarcoma, melanoma, and lymphosarcoma (see Table 66.1). The lymphosarcoma listed is a historic case report from 1890 [11]. In retrospect, the patient may have had a non-Hodgkin lymphoma.

The development of malignant esophageal tumors is generally associated with lifelong exposure to carcinogenic stimuli, which might explain the rarity of these tumors in children. Nevertheless, it is important to remember that certain conditions such as repair of an esophageal atresia or caustic injury to the esophagus during

childhood may lead to cancer in early adulthood. In these cases, a close transition from pediatric to adult medical care is warranted.

Squamous Cell Carcinoma

To date, 20 cases of esophageal SCC in children have been reported [6, 7, 142–150]. A review of these 20 cases shows that the median patient age at diagnosis is 15 years (range, 8–21 years) and that esophageal SCC is almost evenly distributed among boys and girls (M:F = 1.2:1).

The development of SCC has been strongly associated with the consumption of certain foods and food ingredients (e.g., moldy foods, hot beverages, alcohol, cottonseed oil, lye, nitrosamines); *G. candidum* contamination; tobacco use; and low intake of riboflavin, retinol, zinc, and iron. Caustic injury to the esophagus leading to chronic inflammation is one of the strongest risk factors for its development. Although it generally takes decades for malignant changes to develop, three cases of esophageal SCC after caustic injury have been described in pediatric patients [37, 54, 145]. In these cases, esophageal SCC occurred 1, 10, and 12 years after a caustic injury in early childhood. In one case, the caustic injury occurred after lye ingestion. In the remaining two cases, it resulted from unknown caustic agents. Other case reports have mentioned a history of cigarette smoking at a young age, prior chemotherapy for osteosarcoma, a gastric trichobezoar, and esophageal human papilloma virus-16 infection as risk factors for SCC.

We examined the distribution pattern of SCC within the esophagus in these 20 children and found that SCC occurred equally throughout the entire length of the esophagus, without any predilection for a specific esophageal region. Most patients presented with local disease without evidence of metastases. When metastases were present, they were mainly found in the regional lymph nodes. Metastases to solid organs were found in only one patient.

Outcome was reported for 16 of the 20 patients. Ten patients were alive at a median follow-up time of 0.5 years (range, 0–1.7 years). Obviously, longer follow-up will be needed to generate more thorough survival data for these children.

The mainstay of therapy for esophageal SCC is complete resection with wide lymphadenectomy. These 20 patients offer insufficient data to adequately evaluate the effectiveness of different treatment regimens. Thus, it is unclear if adding chemotherapy or radiation therapy to operative resection prolongs survival in pediatric patients with esophageal SCC.

Adenocarcinoma

To date, 17 cases of esophageal AC in children have been reported [6, 9, 36, 38, 49–53, 55, 151, 152]. The median patient age at diagnosis is 16 years (range, 8–20 years). The youngest patient ever diagnosed with esophageal AC was 8 years old [9]. As in adults, the male gender is predominantly affected (M:F = 4.6:1) [153]. Interestingly, the dramatic increase in the incidence rate of esophageal AC in adults over the last few decades has not been observed in children and adolescents [154].

AC is closely linked to the sequence of GERD and the development of BE. Risk factors for esophageal AC in adults commonly include long duration of GERD symptoms, presence of BE, male gender, white race, age, history of smoking, and obesity [153]. Risk factors for esophageal AC in children are not clearly understood. In general, however, the same relationship of GERD and BE with the development of AC is thought to be true for children. Among the 17 cases of childhood esophageal AC, preexisting conditions included spinal palsy, history of esophageal atresia repair, hiatal hernia, obesity, and foreign body ingestion. All of these conditions are known risk factors for GERD and BE in children [155]. In 6 of the 17 cases, BE was actually observed next to the AC [36, 49, 51].

The time span, and thus the chance to develop BE and AC due to GERD, is seemingly short in children. However, it is postulated that GER in infancy can be carried on "silently," leading to problems in later childhood and adulthood [156, 157]. This observation is supported by recent findings

showing that preterm and small-for-gestational-age infants, in whom GERD is common, have a greater than 11-fold risk of developing esophageal AC in adulthood [158, 159].

In cases of familial BE, AC has an earlier onset and a higher rate of malignant transformation than in cases of nonfamilial BE [160]. However, a positive family history of BE has not yet been reported in children and adolescents with AC. It will be interesting to see if ongoing investigations will identify the genes involved in the development of BE and AC [161]. In summary, an early initiation of the GERD-BE-dysplasia sequence and a possible genetic predisposition are most likely the etiological steps for esophageal AC in children and adolescents.

Eleven of the 17 patients developed metastatic disease. Lymph node metastases occurred to the esophageal nodes, the aorta, and the stomach. Two patients had pulmonary metastases, and one had cerebral metastases [6, 152]. Of the 17 patients, 10 (59 %) died after a median follow-up time of 0.8 years (range, 0–3 years). Despite the generally poor outcomes reported for esophageal AC, there are some cases with survival for longer than 24 months [36, 52].

For children with esophageal AC, early diagnosis and aggressive therapy with complete surgical resection are critical for prolonging survival.

Sarcoma

Of all malignant pediatric tumors, 7 % are sarcomas; of these, 2 % occur in the GI tract [162, 163]. Synovial sarcomas rarely occur outside of joint capsules. When they do, they are thought to originate from undifferentiated mesenchymal cells. Three cases of synovial sarcoma of the esophagus in adolescent have been reported [164–166]. The patients presented at 14, 15, and 20 years of age with fairly large tumors in the proximal esophagus in close proximity to the hypopharynx.

Because synovial sarcomas are generally very aggressive, an aggressive treatment approach is warranted. Resection followed by a combination of chemotherapy and radiation therapy offers the only chance of cure, but only in the setting of localized disease [167]. In the three reported cases, the patients received chemotherapy and/or radiation therapy after resection and were disease-free at a median follow-up of 30 months after completion of treatment.

Melanoma

About 200 cases of primary malignant melanoma of the esophagus have been reported in adults [168], but only one case has been reported in a child [8]. In this single case, a 7-year-old boy presented with a lobulated melanoma in the mid-esophagus. Six months after wide resection, the patient lost weight, developed respiratory distress and pneumonia, and died. A highly aggressive malignant melanoma, which had surrounded and invaded the trachea, leading to airway obstruction, was found on autopsy [8].

Typically, melanoma of the esophagus is locally aggressive and disseminates early via the bloodstream and the lymphatics. Even with aggressive therapy, the prognosis of patients with melanoma of the esophagus is poor: the 5-year survival rate is less than 5 % in adults [168].

Conclusion

Esophageal tumors are exceedingly rare in childhood and adolescence. However, they should always be considered when a pediatric patient presents with dysphagia, respiratory compromise, retrosternal pain, failure to thrive, or a combination of these symptoms. Leiomyomatous lesions are the most commonly reported esophageal tumors in pediatric patients followed by SCC and AC. Early diagnosis, based on careful evaluation and diagnostic workup, is warranted for both benign and malignant esophageal tumors to reduce the operative morbidity and to improve outcome. While benign tumors are generally associated with an excellent prognosis, malignant tumors are associated with a devastatingly poor prognosis. Many clinical and laboratory investigations are under way to try

to identify the genetic and pathologic pathways involved in esophageal carcinogenesis, which may help improve the management of children with malignant esophageal tumors.

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Epidermolysis Bullosa: Epidemiology, Diagnosis, Complications, and Treatment

67

Richard G. Azizkhan and Ahmed Mami

Introduction

Epidermolysis bullosa (EB) comprises a wide spectrum of rare genodermatoses of varying severity that are characterized by excessive skin fragility and mucocutaneous blistering in response to minor mechanical friction or trauma. The etiology of these conditions is attributed to mutations in one or more of ten different genes that affect structures that hold together the epidermal and dermal layers of the skin. According to a recently revised classification system developed with international consensus [12], there are four major EB types: EB simplex (EBS), junctional EB (JEB), dystrophic EB (DEB), and Kindler syndrome. Within these classifications, there are subtypes that also vary in both severity and genetic etiology (Table 67.1). Regardless of EB type, patients suffer with a continuous cycle of blistering, scarring, and wound healing that has a devastating impact on quality of life. The inability to take in sufficient calories to maintain an anabolic state in the presence of the increased metabolic demands of constant wound healing or the impact of disease on the esophagus and oropharynx typically leads to compromised nutritional status. Given that nutritional problems are more severe in patients with the recessive DEB subtype (RDEB) and JEB, these patients more commonly require nutrition-related surgical interventions. It is therefore essential for surgeons involved in their care to be knowledgeable as to these EB types in particular, the inherent nutritional issues that these patients face, and their special perioperative needs. To this end, our discussion will provide a succinct description of nutritional issues in RDEB and JEB, subsequently focusing on special needs of this patient population within the context of esophagogastric procedures.

Clinical Overview

Valuable clues as to EB type are often gained by experienced clinicians who become familiar with the various phenotypic expressions seen in EB, as well as the anatomic sites affected and extent and severity of disease.

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Table 67.1 Ultrastructural findings and gene abnormalities among major types and selected subtypes of EB

EB type or subtype	Ultrastructural site of skin findings	Target gene (protein)
EB simplex (*EBS*)		
EBS localized	Basal layer	KRT5 (keratin 5)
EBS DM	Basal layer in subnuclear cytoplasm	
EBS-MD	Predominantly in basal layer, above level of HD attachment plaque	PLEC1 (plectin)
EBS-AR	Basal keratinocytes	KRT14 (keratin 14)
EBS, lethal acantholytic	Suprabasal cleavage and acantholysis	DSP (desmoplakin)
EBS, plakophilin-1 deficiency	Mid-epidermal cell-cell separation	PKP1 (plakophilin1)
EBS-PA	Lower basal layer, above level of HD plaque	PLEC1 (plectin)
Junctional EB (*JEB*)		
JEB-H	Lamina lucida	LAMA3, LAMB3, LAMC2 laminin 332
JEB-nH	Lamina lucida	LAMA3, LAMB3, LAMC2 laminin 332, COL17A1 (type XVIII collagen)
JEB-PA	Lamina lucida	ITGA6, ITGB4 (α6β4 integrin)
Dominant dystrophic EB (*DDEB*)		
DDEB, generalized	Sub-lamina densa	COL7A1 (type VII collagen)
DDEB-BDN	Sub-lamina densa	
Recessive dystrophic EB (*RDEB*)		
RDEB, severe generalized	Sub-lamina densa	COL7A1 (type VII collagen)
RDEB, generalized other	Sub-lamina densa	
RDEB-BDN	Sub-lamina densa	
Kindler syndrome	Multiple cleavage planes (intradermal, junctional or sub-lamina densa)	KIND1 (kindlin 1)

AF Anchoring fibril, *AR* autosomal recessive, *BDN* bullous dermolysis of the newborn, *DM* Dowling-Meara, *H* Herlitz, *HD* hemidesmosome, *MD* muscular dystrophy, *nH* non-Herlitz, *PA* pyloric atresia, *SBDP* subbasal dense plate

RDEB

The incidence of RDEB in the United States (US) is estimated at 2.04 per million, with a carrier frequency of 1 in 345 [26]. RDEB has been linked to mutations in the *COL7AI* gene, which resides on the short arm of chromosome 3 [31]. It is not uncommon for these mutations to occur de novo [32]. The *COL7AI* gene codes for type VII collagen, which is a major component of the anchoring fibrils responsible for epidermal-dermal adhesion beneath the basement membrane within the papillary dermis of skin and mucous membranes [9, 33]. This abnormality manifests in frequent blistering in areas of friction, which may result in extremity contractures that eventually lead to pseudosyndactyly in the hands and feet (Fig. 67.1). Repetitive injury often leads to aggressive squamous cell carcinomas in the third decade of life.

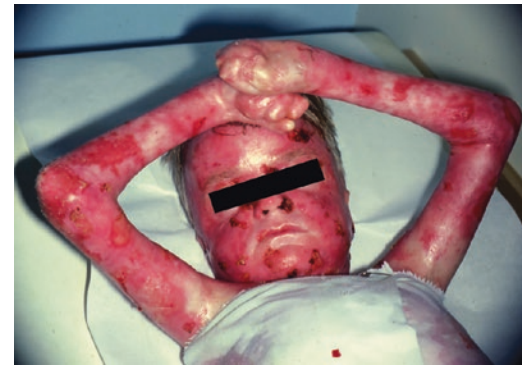

Fig. 67.1 Child with severe generalized RDEB. This patient has significant pseudosyndactyly, contractures, growth and nutritional failure

Because of the high nutritional demands of continuous inflammation and wound healing and difficulty with adequate intake due to oral and esophageal blistering and scarring, children with

RDEB generally have an array of nutritional problems [1, 5, 23]. In many patients, poor nutrition leads to anemia, failure to thrive, growth retardation, osteopenia, osteoporosis, and, rarely, dilated cardiomyopathy [13]. Nutritional deficits often involve a vitamin and trace metal deficiency that is not always correctable with enteral caloric supplementation [18]. Lip and oral mucosal involvement may lead to the development of progressive microstomia and subsequent ankyloglossia, rendering oral feeding problematic and painful. By 12 years of age, more than 50 % of RDEB patients suffer with both of these conditions [11]. Repeated blistering and scarring in the esophagus and oropharynx may lead to esophageal strictures [3, 4, 6, 17]. According to the National EB Registry, more than 90 % of patients eventually develop these strictures, and they are seen in patients as young as 18 months of age. Over time, esophageal strictures may lead to progressive dysphagia or odynophagia. If untreated, patients may even have difficulty swallowing their own saliva. Additionally, many patients suffer from constipation, resulting from painful defecation due to perianal skin involvement and fissures, dehydration from decreased oral intake, ongoing fluid loss through chronic wounds, and chronic ingestion of narcotic analgesics. In view of these numerous and complex issues, it is not surprising that up to 77 % of children with RDEB are at risk for significant malnutrition [5]. As such, every effort must be made to alleviate the array of distressing problems. Appropriate interventions can be accomplished only through the collaborative efforts of a multidisciplinary team of experienced professionals.

Although aggressive supportive therapy, including esophageal dilatations, allows most patients to maintain adequate nutritional status, approximately 25–30 % of patients require placement of a gastrostomy tube [29]. These interventions are discussed later in the chapter.

JEB

The estimated incidence of JEB in the United States is 2.04 per million, with a carrier frequency of 1 in 333 [26]. Mutations have been linked to four genes: *LAMB3* (70 % of all JEB), *COL17A1* (12 %), *LAMC2* (9 %), and *LAMA3* (9 %) [27].

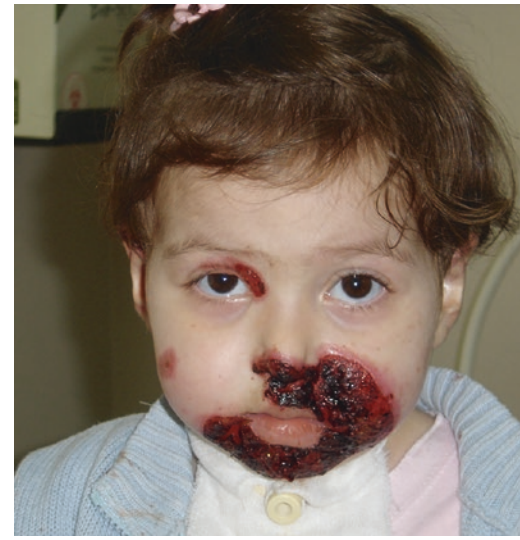

Fig. 67.2 Small child with JEB Herlitz type. This child has a tracheostomy for airway involvement. The severe facial granulation tissue is a characteristic manifestation of this disorder

In several JEB subtypes (e.g., Herlitz), the physical manifestations of disease are extremely severe and may affect the respiratory tract, resulting in death during early childhood (Fig. 67.2). Despite tracheotomy placement, these patients may succumb to progressive airway obstruction. Some patients have bladder and kidney involvement and may require urological procedures. Pyloric atresia (PA) has also been identified (JEB-PA) and is often lethal in the neonatal period. Most patients with the non-Herlitz generalized subtype survive into adulthood. Although these patients may have nutritional issues, they are not as severe as those seen in patients with RDEB. In contrast to the high risk for malnutrition (77 %) in children with RDEB, research indicates that only 57 % of children with JEB are at risk [5]. Our own experience reflects this finding, as most of our patients who require surgical intervention for nutritional issues have RDEB.

Diagnostic Approaches

Laboratory approaches to the diagnosis of EB include transmission electron microscopy (EM) and immunofluorescence mapping (IFM). Both of these approaches allow determination of the

diagnostic level of skin cleavage. EM offers the advantage of permitting visualization and semi-quantitative assessment of specific structures (e.g., anchoring filaments and fibrils, keratin filaments, desmosomes, hemidesmosomes, and subbasal dense plates), which are known to be altered in number or appearance in certain EB subtypes (Table 67.1) [12].

IFM is the primary laboratory technique for confirming the diagnosis of EB. Many laboratories exist worldwide that properly perform this technique using a series of EB-relevant antibodies and well-established protocols. Moreover, IFM is relatively inexpensive and comparatively quick and easy to perform.

Mutational analysis provides a means of determining the mode of inheritance and the precise site(s) and type(s) of molecular mutation present in a patient. We now have the capability of using this technique for prenatal and preimplantation diagnosis [7, 10].

Assessment of Esophageal Strictures

Before undergoing dilatation, all EB patients should have a thorough medical examination and nutritional assessment. Patients presenting with dysphagia, nutritional deficiency, or poor weight gain should have a contrast esophagram performed to assess the status of their esophagus and the presence and number of strictures. The inclusion of the pharyngoesophageal junction in this study is crucial, as many patients with RDEB have a high cervical esophageal stricture that can be missed on a routine esophagram (Fig. 67.3). The proximal cervical esophagus is the most common location for strictures. Based on a recent analysis, this is seen in approximately 85 % of our RDEB patients; approximately 40 % have more than 1 stricture [3]. Dilatations are performed initially only when the stricture is radiologically confirmed. A barium esophagram delineates the number, level, and severity of the strictures, thereby providing a roadmap for the dilatation procedure. This study should incorporate frontal and lateral projections and must assess the entire esophagus from the oropharynx through to the gastroesophageal junction.

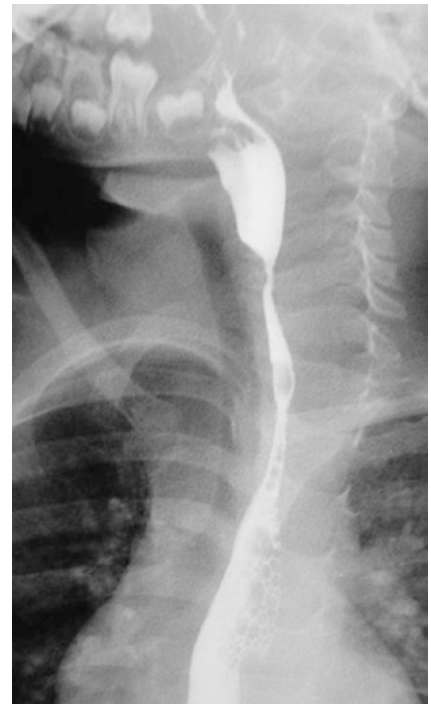

Fig. 67.3 Barium esophagram outlining proximal esophageal stricture at C4 in a patient with RDEB

Preoperative Evaluation

Optimally, EB patients and their families should be seen within 2 weeks of a scheduled surgical procedure. This permits data collection and evaluation to be carried out in an unhurried manner, avoiding the risk of last-minute preparation delays. A thorough overall assessment consists of a number of critical components, including airway, cardiac, and positioning evaluations, as well as appraisal of the readiness for anesthesia induction [15].

Airway Assessment

Airway assessment should focus on five areas of concern. First, both the vertical and horizontal aspects of the mouth opening may be limited.

This, together with an overbite, can make traditional laryngoscopy and intubation impossible to perform. Limiting mouth opening becomes more of an issue as EB patients approach adolescence, though it can occur earlier. The second area of focus is dentition. This can be poor, with multiple caries and overcrowding of the teeth [8, 34]. Third, skin fragility requires that utmost attention be paid to manipulation of the face, buccal mucosa, and gums during airway management and that preexisting lesions be noted. Fourth, the severity of ankyloglossia should be noted. This condition may be pronounced, such that the patient may have minimal to no tongue movement. Despite anatomic limitations and potential difficulties in intubating these patients, mask ventilation is often maintained without difficulty. The fifth area of concern is the possible presence of glottic stenosis, which may have occurred as a result of prior airway manipulations; this condition further compromises the ability to secure the airway. Patients with JEB (Herlitz generalized) are at higher risk for subglottic stenosis, as well as choanal and nasal stenosis, and excessive peritracheal and intranasal granulation tissue [21].

Cardiac Evaluation

Several studies demonstrate an increasing body of evidence for dilated cardiomyopathy in patients with RDEB [13, 25, 28]. Although the cause remains unclear, selenium or carnitine deficiencies have been implicated as a possible etiology. In view of this evidence, we advise that patients with RDEB who will be undergoing surgery and require anesthesia should have an echocardiogram within 12 months prior to surgery. If significant findings are present, it is prudent to repeat the exam closer to the scheduled date of surgery. Unfortunately, beyond standard measures for the treatment of dilated cardiomyopathy and improving nutritional status, there is no method of optimizing cardiac function. Nonetheless, this evaluation enables more accurate risk assessment and perioperative planning.

Positioning Evaluation

To ensure proper positioning, extensive or painful wounds or blisters should be noted. Because many EB patients have joint contractures as well skin lesions, improper positioning increases the risk of further skin damage.

Induction Readiness

Given that a smooth, atraumatic induction is optimal, the clinician should attempt to determine whether the patient is likely to be compliant with induction. Parental presence at induction is extremely helpful and should be encouraged. In patients who are extremely anxious, we routinely use oral midazolam to facilitate a smooth induction.

Esophagogastric Procedures

Esophageal Dilatation

Overview

Although intensive nutritional support is often sufficient to maintain the metabolic status quo, esophageal dilatations enhance the patient's ability to tolerate oral feeds and should thus be performed when necessary. Our clinical experience suggests that as many as 80 % of patients with RDEB have symptomatic strictures requiring esophageal dilatation by age 25. Historically, patients who underwent esophageal dilatations for strictures had some form of bougienage performed blindly with tapered mercury-filled rubber Maloney dilators or serial Tucker dilators pulled through a gastrostomy with the aid of a string guide. These techniques were associated with postoperative pain, extensive esophageal mucosal sloughing, and often, a prolonged period of recovery during which adequate oral intake could not be resumed.

In view of the poor outcomes, such techniques have been supplanted by endoscopically and fluoroscopically guided hydrostatic balloon dilatation techniques [2, 6, 17]. Owing to the fact that

some degree of mucosal shearing of the pharyngoesophageal region is inherent in endoscopically guided dilatation, this approach may result in a greater degree of mucosal blistering and sloughing than a nonendoscopic approach. To reduce the potential for iatrogenic sheer stress injury to the esophagus, we employ a nonendoscopic balloon dilatation technique. This has become our technique of choice for EB patients with symptomatic esophageal strictures. It permits a more specific anatomic identification of length and severity of the stricture(s) than does an endoscopic approach. Also, it allows for the use of much larger balloon sizes, achieving larger functional esophageal diameter. Most important in regard to quality of life, the nonendoscopic approach results in a longer interval between dilatations. Nevertheless, both dilatation techniques relieve distressing symptoms and effect dramatic changes in social behavior and the ability to enjoy food [4].

Cincinnati Esophageal Dilatation Technique

In the interventional radiology suite, using fluoroscopy, we initially place an 8-French umbilical artery catheter (Boston Scientific Corp., Natick, MA) transorally into the upper esophagus (Fig. 67.4a). We then pass a flexible soft-tip Benson 0.035-in guidewire (Cook Inc., Bloomington, IN) into the stomach through the catheter (Fig. 67.4b). Once the position of the guidewire is fluoroscopically verified, it remains in place throughout the entire procedure. The umbilical artery catheter is removed (Fig. 67.4c). The high-pressure hydrostatic balloon catheter is then placed over the guidewire into the distal esophagus (Fig. 67.4d). The balloon length and diameter depend on the age and size of the patient as well as the characteristics and number of strictures that are present. Balloon length typically varies from 6 to 8 cm; balloon diameter varies from 12 to 22 mm. We begin by inflating the balloon with a 50 % dilution of Optiray 240 water-soluble contrast (Mallinckrodt Inc., St. Louis, MO) centered over the most distal stricture (Fig. 67.4e). The initial portion of the injection is performed manually with a Bard Balloon Inflation System syringe (CR Bard Inc., Billerica, MA) with a built-in manometer. This is subsequently locked and the handle turned clockwise to apply a gradual increase in balloon pressure until stricture effacement has occurred (up to approximately 2 atmospheres) (Fig. 67.4f). The pressure applied must be kept less than balloon burst specifications at all times. Simultaneous fluoroscopy allows visualization of the stricture(s) and their gradual effacement as dilatation progresses. The center of the balloon must be placed at the midpoint of the stricture to prevent cephalic or caudal migration of the balloon, which could result in shearing forces on the esophageal mucosa. Aboral (caudal) migration of the balloon is prevented by applying gentle traction to the balloon catheter during balloon inflation. The balloon is left inflated for up to 30 s before deflation and repositioning to dilate other more proximal strictures. A small amount of contrast left within the balloon can facilitate the identification of additional strictures within the esophagus, as narrowing can clearly be seen on retracting a partially inflated balloon (Fig. 67.5a, b). It is important to perform this esophageal mapping maneuver up to and including the pharyngoesophageal junction in order to avoid missing high strictures commonly found in RDEB, which may not have been picked up on a routine contrast esophagram. We then replace the balloon catheter with the previously used umbilical artery catheter over the guidewire with the purpose of performing a limited contrast esophagram. This procedure can help confirm satisfactory patency of the esophageal lumen after dilatation and also rules out esophageal perforation. For this purpose, we use standard Optiray 240 injected through the umbilical artery catheter as it is withdrawn from distal to proximal during fluoroscopy. Any residual contrast is then aspirated from the esophagus to reduce the postoperative risk of contrast aspiration. In some patients with a difficult airway, masked ventilation can be used, and a retrograde esophageal dilatation can be achieved using as gastrostomy stoma. In this subgroup of patients, we perform the dilatation process from the proximal to the distal esophagus.

Postoperative Management

Once patients are safely recovered and awake, they resume a liquid diet. This is followed by a soft diet as tolerated. Patients who have undergone dilatation for the first time are usually monitored overnight in hospital and discharged home on the following day. Those who have previously undergone dilatation at our institution are discharged within 8 h. In an effort to delay recurrent stenoses, we routinely administer perioperative and postoperative steroid treatment. Patients receive 0.5 mg/kg of dexamethasone with a maximum dose of up to 20 mg intravenously at induction. This is followed by a 5-day tapered dose of liquid prednisolone that is started at 1–2 mg/kg. To minimize the effects of acid gastroesophageal reflux, we also prescribe a proton pump inhibitor. Patients who require repetitive dilatations remain on this regimen indefinitely.

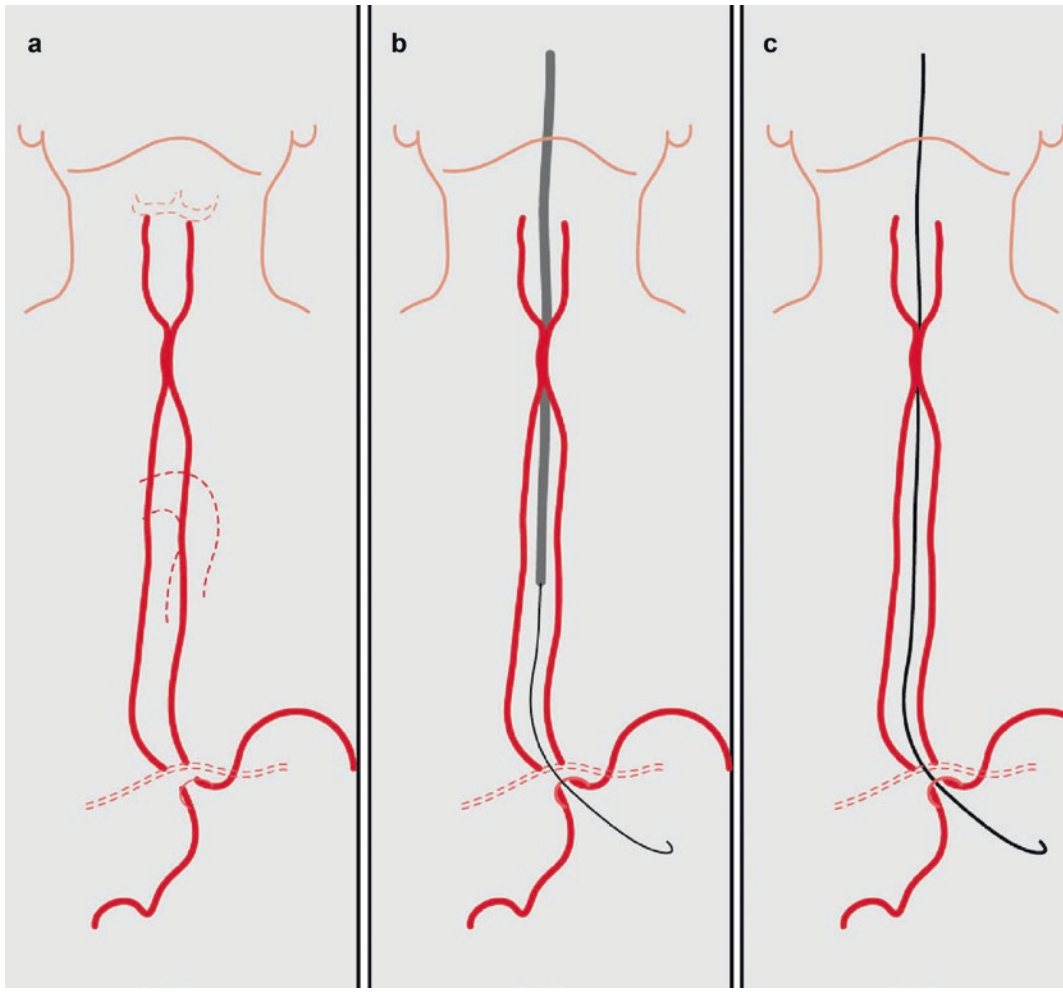

Fig. 67.4 The illustration depicts the sequential steps in performing the nonendoscopic hydrostatic balloon dilatation using fluoroscopic guidance. (**a**, **b**) An 8-Fr. umbilical catheter with a flexible soft guidewire is inserted through the oropharynx and positioned past the strictured esophagus. (**c**) The umbilical catheter is removed leaving the guidewire in place. (**d**) The hydrostatic balloon catheter is placed over the guidewire and positioned at the level of the stricture(s). (**e**, **f**) The balloon is insufflated with water-soluble contrast under fluoroscopy. Initially the stricture appears as a narrow waist. With gentle insufflation pressure (1–2 atmospheres), the stricture is effaced

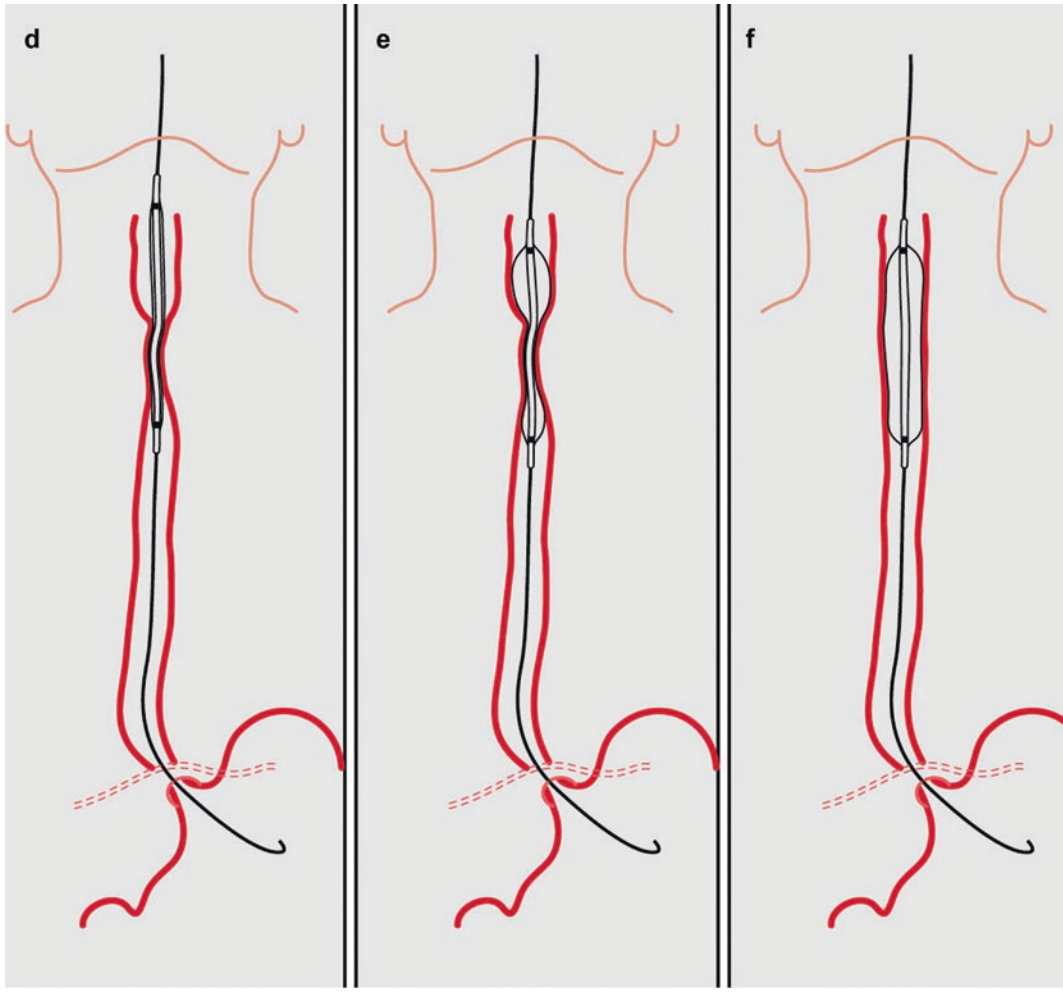

Fig. 67.4 (continued)

Our Outcomes

To date, we have performed 500 fluoroscopically guided hydrostatic balloon dilatations on more than 150 patients with RDEB over an 18-year period (1993–2010). The mean age of our patients at first procedure is 10 ± 8 years (range 1.5–40 years). Sixty percent of patients have had a solitary stricture, and 40 % have had two or more strictures; 85 % of these strictures have been in the proximal esophagus. Balloon diameter has varied from 12 to 22 mm, with a median diameter of 18 mm.

Most of our patients have experienced immediate relief of their symptoms and have been able to resume a normal diet within 24 h of the procedure. All have had significant weight gain 4–6 weeks after dilatation. The mean interval between dilatations has been 1 year, with a range of 1.5 months to 6 years. The median follow-up time has been 7 years (range 1–15 years). Using this technique, we have not encountered any dilatation-related esophageal perforations. Two patients who had dental procedures performed under the same anesthetic developed aspiration postoperatively and required antibiotics and intensive respiratory therapy; they both made a satisfactory recovery.

Radiation and Dilatation

The risks of repeated radiation exposure in EB patients subjected to frequent dilatations must be

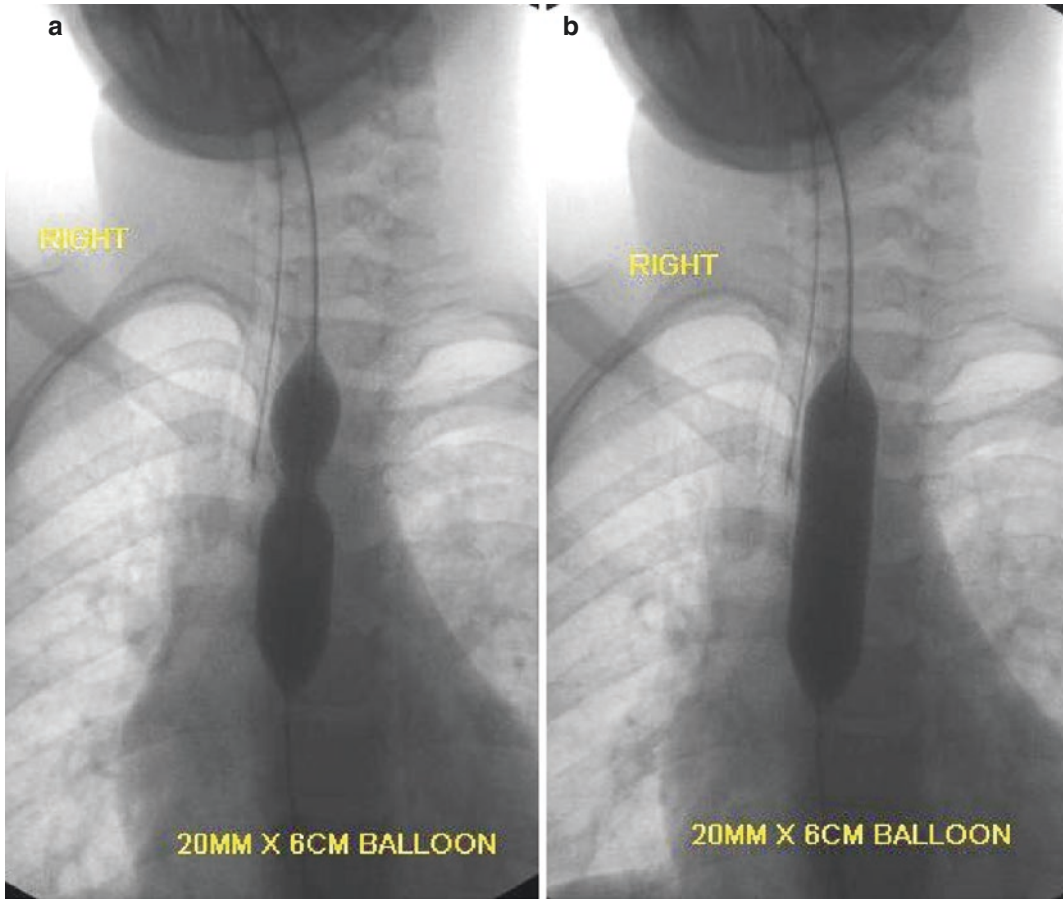

Fig. 67.5 Balloon dilatation of proximal esophageal stricture in a child with RDEB. (**a**) Balloon demonstrates stricture with a narrow waist. (**b**) Effacement of stricture with hydrostatic balloon catheter

balanced against the quality of life achieved from this intervention. Because of the increased risk of squamous cell skin carcinoma in EB patients [22], this is particularly important. It prompts us to adhere to strict radiation protection methods and to be vigilant for early signs of malignancy.

Gastrostomy Tube Placement

Overview

For some (25–30 %) patients, dilatations are not sufficient to counter the effects of nutritional compromise, and placement of a gastrostomy tube for enteral feeding is required [24, 29]. A number of approaches for gastrostomy tube placement have been used successfully. Either open or percutaneous gastrostomy can be performed, with the latter carried out using either an endoscopic or nonendoscopic technique. After gastrostomy tracts have healed and are well established, original tubes can be replaced with low-profile gastrotomy buttons.

When oral intake is insufficient, gastrostomy tube placement guarantees an enteral feeding route and helps to reduce constipation by ensuring adequate hydration. Nevertheless, it also has several disadvantages. It is not always well accepted in teenagers and adults, and many dislike the need for button change. Further, leakage and irritation can occur around the gastrostomy site, incontinence can occur with overnight feeding, and gastroesophageal reflux can worsen [24].

Spectrum of Techniques

The standard open approach with a Stamm gastrostomy is an excellent means of obtaining prompt, secure access to enteral feeding. We use this approach in almost all patients up to the age of approximately 18 months. In this procedure, we use a small upper midline incision, bringing the gastrostomy tube out through a separate paramedial opening in the abdominal wall. Given that the stomach is anchored to the abdominal wall, changing to the button gastrostomy tube can be accomplished within a few weeks.

The other techniques commonly used for gastrostomy insertion include percutaneous endoscopic gastrostomy (PEG) or laparoscopically assisted gastrostomy. Both of these procedures have potential drawbacks. Although PEG insertions are generally a safe and efficient means of obtaining gastric access, an endoscope can contribute to inadvertent esophageal trauma. Although not formally described in the literature, a theoretical drawback of laparoscopically assisted gastrostomy is that peritoneal insufflation with gas distends the abdomen, stretching the overlying skin. This may result in severe blistering and subsequent skin loss with associated pain and wound issues. In view of these considerations, we now employ the "push" technique of nonendoscopic percutaneous gastrostomy for patients older than 18 months of age.

Nonendoscopic Percutaneous Gastrostomy Placement ("Push" Technique)

Potential candidates for nonendoscopic gastrostomy placement must undergo a preoperative assessment with a contrast esophagram and upper gastrointestinal series to look for esophageal strictures and the size and orientation of the stomach. The presence of microgastria or a high-lying stomach makes them unsuitable for this approach, and alternative methods of gastrostomy placement must be used.

In performing this procedure, the edges of the liver and spleen are mapped out with ultrasound and marked on the patient's skin. The transverse and descending colon are outlined by the instillation of 100–150 mL of dilute water-soluble contrast via a rectal catheter under fluoroscopic control. An 8-French umbilical catheter is then passed through the oropharynx into the stomach, and 100–150 mL of air is insufflated radiographically to delineate the stomach. Before gastric insufflation, 0.1 mg of glucagon is administered intravenously to provoke pylorospasm, thereby reducing the amount of air passing into the duodenum during the procedure. The procedure is facilitated by the availability of anteroposterior and cross-table fluoroscopic guidance for gastrostomy tube placement (Fig. 67.6). Three or four needle-mounted T-fasteners are percutaneously passed into the air-filled stomach in a triangular configuration to pull the stomach up against the anterior abdominal wall. The stomach is then percutaneously cannulated with a needle through the midpoint of the T-fasteners. A small amount of water-soluble contrast is injected through the needle cannula to confirm its location within the stomach. A guidewire is then inserted through the needle cannula, and the needle is removed, leaving the guidewire in place. Over the guidewire, the tract is serially dilated to permit the placement of a 16- to 20-French peel-away sheath (depending on the size of the gastrostomy tube to be placed). A 12- to 16-French MIC® (Kimberly Clark-Ballard, Draper, UT) gastrostomy tube with external silicone flange is inserted through the sheath, and the balloon is inflated with sterile water. The T-fasteners are then tied down to anchor the gastrostomy tube flange to the abdominal wall. Each 3/0 nylon suture (mounted to the T-fastener) is passed through a layer of Mepilex® (Mölnlycke Healthcare, Göteburg, Sweden), a dental roll, and the holes in the flange, thus avoiding the placement of skin sutures and enabling anchorage of the entire gastrostomy system to the abdominal wall. A silk tie is then placed around a groove in the flange to prevent the tube and balloon from slipping inward [24, 29].

Postoperative Management

Gastrostomy feeds are begun the following morning, after the tube has been left overnight to drain into a Farrell bag reservoir (Corpak Medsystems Inc, Wheeling, IL). Once patients are established on an enteral feeding regimen (usually 48–72 h postoperatively), they are discharged. The T-fasteners are left in place for 10–12 weeks. For

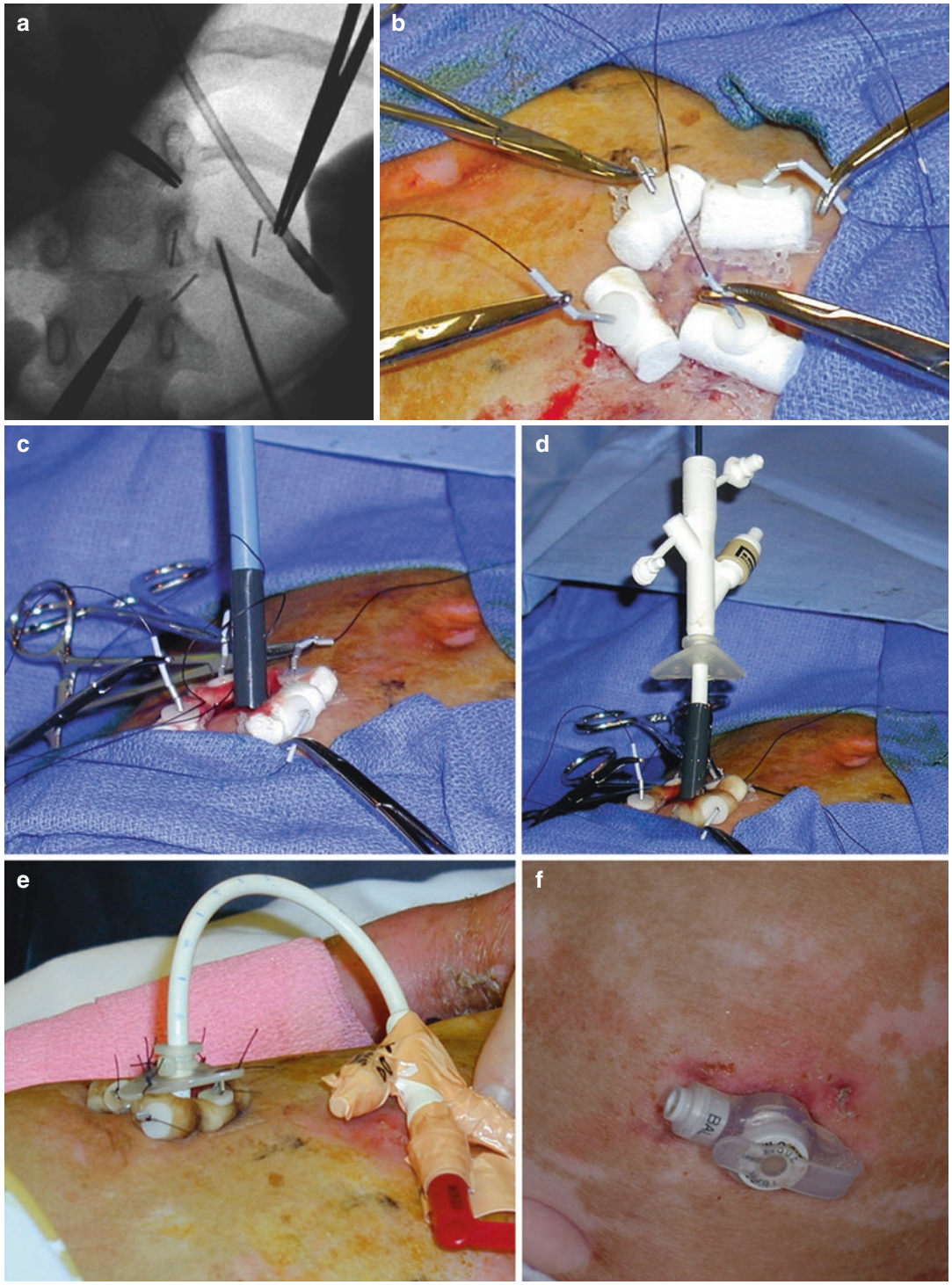

Fig. 67.6 Nonendoscopic percutaneous gastrostomy technique. (**a**, **b**) Percutaneous placement of T-fasteners to anchor stomach to the overlying abdominal wall. Needle will pass into the stomach to permit placement of a guide wire. (**c**) With gentle traction on the T-fasteners, the stomach is cannulated and the tract sequentially dilated to accommodate a large peel-away sheath. (**d**) The gastrostomy tube is placed through the sheath, and the balloon is inflated. (**e**) The catheter and stomach and abdominal wall are secured as a unit by tying the T-fasteners through the flange and securing the flange to the gastrostomy tube. (**f**) Gastrostomy tube site following removal of the initial tube and replacement with a low-profile button gastrostomy

removal, a slight amount of traction is placed on the T-fastener. Concurrently, the gastrostomy tube is replaced with a low-profile button gastrostomy. The T-fastener is then cut flush with the skin while maintaining traction. The gastrostomy stoma can be dressed with a small piece of cut Mepilex® placed between the button gastrostomy and the patient's skin.

Our Outcomes

We have performed nonendoscopic percutaneous gastrostomy tube placement in nine patients (age range 4–9 years) with RDEB. All of these patients had undergone multiple dilatations for esophageal strictures, and every effort had been made to optimize their nutritional status with maximal caloric intake. Despite these measures, they all had persistent growth failure.

All nine patients tolerated the procedure well; all commenced feeds on postoperative day 1; and all had successful gastrostomy button placement at 10–12 weeks postoperatively. Balloon migration obstructing the pylorus occurred in one patient. This complication was attributed to failure to tie the silk suture around the flange and was relieved by repositioning the gastrostomy tube. No other complications were encountered. Two of the nine patients have had subsequent retrograde esophageal dilatation performed through their gastrostomy without difficulty. To date (June 2010), the average follow-up in this group of patients has been 48 months (range 1–9 years). All patients have shown significant gains in weight and height. In addition, parents have noted higher energy and activity levels in their children, as well as less severe blistering and more rapid wound healing than seen before the procedure. As well, we have been able to administer medications more reliably.

Perioperative Care for Esophageal Interventions

The special needs of EB patients mandate comprehensive preoperative planning and assiduous perioperative care. To minimize skin trauma, we place patients on an eggcrate foam mattress before any surgical procedure. To lessen anxiety and decrease unnecessary movement, we generally administer oral midazolam preoperatively. In that skin lesions, low body mass index, and lack of subcutaneous fat predispose patients to the risk of heat loss, warming the operating room is crucial [15].

The surgical team must be cognizant of the fact that simply holding and sealing a facemask on the patient's face can cause serious skin damage under the mandible and around the mouth. Avoiding such complications requires lubricating masks, gloves, and instruments (including the laryngoscope blade) with Aquaphor ointment (Beiersdorf Inc, Wilton, CT) or a similar lubricant.

Because of repeated blistering and scarring, establishing peripheral venous access can be difficult. Our preference is thus to induce anesthesia by mask with inhalation anesthetics. If gaining peripheral intravenous (IV) access is difficult, we use ultrasound guidance and interventional radiology to facilitate IV placement. The skin must be protected from tourniquet and blood pressure cuff application by the placement of layers of gauze or Webril® (Tyco Healthcare, Mansfield, MA) on the skin initially. IV lines should be secured with an atraumatic soft silicone adhesive dressing such as Mepitac® (Mölnlycke Healthcare, Göteburg, Sweden) and gently wrapped with Webril® and Coban wrap (3M, St. Paul, MN). The eyes are lubricated and covered with saline-moistened gauze or taped closed with atraumatic Mepitac tape (Mölnlycke Healthcare, Göteburg, Sweden). The adhesive pulse oximeter probe that is commonly used in pediatric anesthesia is exchanged for a clip-type probe that can be placed on the ear lobe. Alternatively, the adhesive can be removed from the probe, and the probe can be secured in place by using the thin malleable metal strip commonly found in the nosepiece of a surgical facemask. The adhesive rim of electrocardiographic leads should be removed. The leads should be applied to a clear portion of skin on the chest and secured in position with Mepiform® or Mepitac®.

The importance of managing a potentially difficult airway in the setting of fragility of the skin and mucous membranes cannot be overemphasized [19, 20]. Oral airways should be used with caution, if at all, due to the risk of mouth and airway blistering. When possible, we perform endotracheal anesthesia. In patients with microstomia, the tongue is often scarred down to the floor of the mouth, and the teeth are often angled inward, making endotracheal intubation more difficult. All of these factors may necessitate an oral fiber-optic intubation. The endotracheal tube is secured with lubricated cotton tape tied to the tube and placed behind the patient's neck after a protective layer of Mepilex® or Mepilex Lite® has been placed on the skin to avoid traction or shearing forces of the tape on the skin.

Esophageal Replacement

For more than 35 years, esophageal replacements have been rarely performed for severe and recalcitrant esophageal strictures in patients with RDEB [16, 30]. The vast majority of these were colonic interpositions. In a recent analysis of the National Epidermolysis Bullosa Registry of 3,280 EB patients, only 16 patients had colonic interpositions [14]. All of these patients had a subtype of RDEB and accounted for less than 5 % of the RDEB patients in the registry. While reported complication rates and mortality for non-EB patients undergoing colonic interposition are a significant 30 % and 3 %, respectively, there is inadequate published data as to outcomes with this group of EB patients. However, Fine et al. report that EB patients who have had a successful interposition seem to do well and are satisfied with their ability to maintain adequate enteral intake [14].

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Part XII

The Gastroesophageal Junction

Lower Esophageal Sphincter: Normal Structure and Function

68

Osvaldo Borrelli and Nikhil Thapar

Introduction

The esophagus acts as a conduit for the coordinated transport of food from the mouth to the stomach. Developmentally, it can be identified as a distinct structure from 4 weeks of gestation. At birth, it has a length of approximately 8 cm, which doubles in the first years of extrauterine life. Each of the three germ layers (endoderm, ectoderm, and mesoderm) is responsible for esophageal development, and their interactions are crucial for the development of the mucosa, muscular coats, and intrinsic nervous system.

Although the esophagus is capable of peristalsis during the first trimester of gestation, more complex patterns of esophageal motility are detected during the second trimester. By birth, motility of the esophagus functionally consists of three regions, corresponding to the upper esophageal sphincter (UES), body of the esophagus, and lower esophageal sphincter (LES). This chapter relates to the normal structure and function of the LES.

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The Lower Esophageal Sphincter

Normal Anatomy and Function

The lower esophageal sphincter (LES) is a complex high-pressure zone localized at the esophagogastric junction, which regulates the flow of contents between the esophagus and the stomach (Fig. 68.1). Intrinsic smooth muscle fibers of the distal esophagus (LES) constitute the intrinsic active component of the sphincteric mechanism at the esophagogastric junction, whereas the skeletal muscle of the diaphragm represents the extrinsic active component [1]. Since the two components are anatomically superimposed and anchored to each other by the phrenoesophageal ligament that extends from the inferior diaphragmatic surface to the distal esophagus, the LES and crural diaphragm function as a well-coordinated and efficient functional unit. The muscles of the LES are thicker than those of the adjacent esophagus and are not completely arranged in a circular fashion. Distally, they are split into two segments: one straddles the greater curvature and is parallel to the sling fiber of the stomach, and the other consists of short clasps that straddle the lesser curvature and join the gastric sling fibers, which play a key role in the formation and modulation of the angle of His [1]. The LES is tonically contracted at rest to produce a roughly concentric occlusion. However, the occlusion is not perfectly uniform, showing a radial asymmetry

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[2]. In adults, the LES is 2–4 cm long, whereas in children its length increases with age, ranging from few millimeters in newborns to adult values in adolescents [3, 4]. In adults, as in older children, the proximal 1.5–2 cm of the sphincter is above the squamocolumnar mucosal junction and completely encircled by the crural diaphragm, whereas the distal 2 cm is below the squamocolumnar mucosal junction [1]. Consequently, the proximal part of the sphincter lies in the esophageal hiatus and the distal 2 cm in the abdominal cavity. Sphincteric exposure to high intra-abdominal pressures is likely to contribute to the maintenance of EGJ competence. At 8 weeks of gestation, the abdominal portion of sphincter is wide and large; gradually, it shortens so that in newborns the intra-abdominal portion of the sphincter is very short or completely absent, predicting the increased possibility of developing gastroesophageal reflux [3]. Other mechanisms explaining the greater frequency of gastroesophageal reflux in infants include the less oblique angle of insertion of the esophagus into the stomach. However, the exact role of these predisposing factors in determining GER in infants is still largely unknown [5, 6].

Afferent sensory information from the LES to the brain runs in both spinal and vagal sensory afferents. Spinal afferents have their cell bodies in the dorsal root ganglia at T1–L3, whereas vagal afferents have cell bodies in the nodose ganglia [1, 7, 8]. The afferent stimuli travel to the sensory nucleus (NTS), which is closely connected with the dorsal root (DMN) of the vagus nerve [1, 7, 8]. The latter provides parallel inhibitory and excitatory motor innervation to the LES. The rostral neurons in the DMN preferentially give rise to the innervation of the excitatory vagal pathway, whereas neurons in the caudal regions give rise to the inhibitory vagal pathway [8]. Excitatory preganglionic neurons are cholinergic in nature and synapse on postganglionic nitrergic inhibitory neurons localized in the myenteric plexus [8]. Inhibitory preganglionic neurons are also cholinergic in nature and synapse onto postganglionic cholinergic excitatory neurons localized in the myenteric plexus [8]. Myenteric motor neurons to the LES are also innervated by postganglionic sympathetic neurons. However, the vagus nerve exerts the main regulatory action on the LES, whereas sympathetic neurons exert only a modulatory role [1, 7, 8].

One of the main functions of the LES is to create a high-pressure zone for preventing retrograde movement of gastric content into the esophagus. The LES is tonically contracted at rest (Fig. 68.1), exhibiting both radial and axial pressure asymmetries [9]. The LES resting tone is determined by three influences (Fig. 68.2): myogenic properties of sphincteric smooth muscle cells, which are independent of any neural influences and may be produced by ionic movement (i.e., calcium) through smooth muscle cell membranes; cholinergic excitatory activity; and nitrergic inhibitory activity [4, 10]. Excitatory cholinergic neurons and the tonic myogenic property of the LES stimulate contraction, whereas the inhibitory nitrergic pathway favors relaxation [10]. Thus, the net balance between these influences determines the final resting pressure of the LES.

LES pressure is influenced by several factors (Table 68.1). It is significantly variable during the interdigestive migrating motor complex (MMC) cycle. There is a pattern of LES contraction closely related to the phase of MMC in the stomach, showing higher LES pressure during MMC phase III than in phase I [11]. Postprandial LES pressure is rather constant at a level comparable with that measured during phase I of the MMC [11]. LES pressure also shows inspiratory augmentation due to contraction of the crural diaphragm encircling the sphincter [1]. LES pressure is also modified by intra-abdominal pressure, gastric distension, peptides, hormones, various foods, and many drugs [4, 10].

During swallowing and belching, the LES promptly relaxes in order to allow the passage of ingested food or air in appropriate directions (Fig. 68.3). At the time of swallowing, the LES relaxes promptly in response to the initial neural discharge from the swallowing center in order to minimize resistance to flow across the esophagogastric junction [1]. This relaxation starts within 2 s after the peristaltic contraction has begun in the

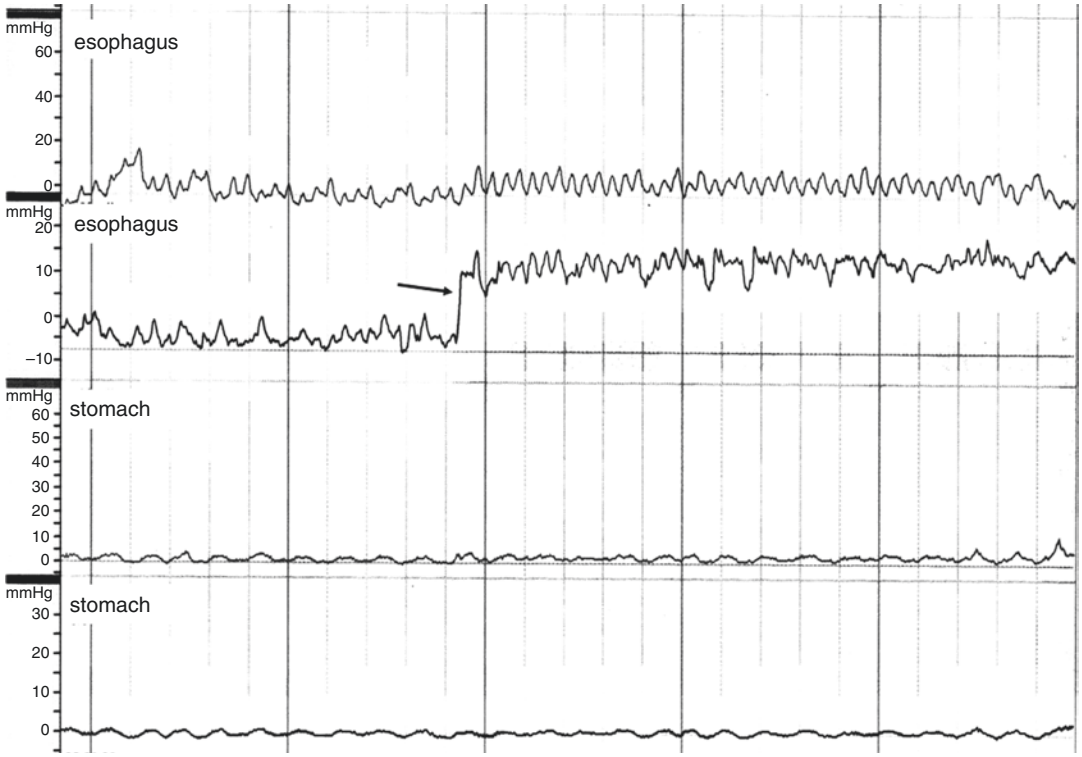

Fig. 68.1 Manometric tracing at the level of the distal esophagus and stomach. From *top* to *bottom*: distal esophagus (first channel), lower esophageal sphincter (second channel), stomach (third and fourth channels). At the level of the second channel, there is a sudden rise in the pressure profile (*arrow*) corresponding to the entrance of the recording side hole of a manometric catheter into the lower esophageal sphincter

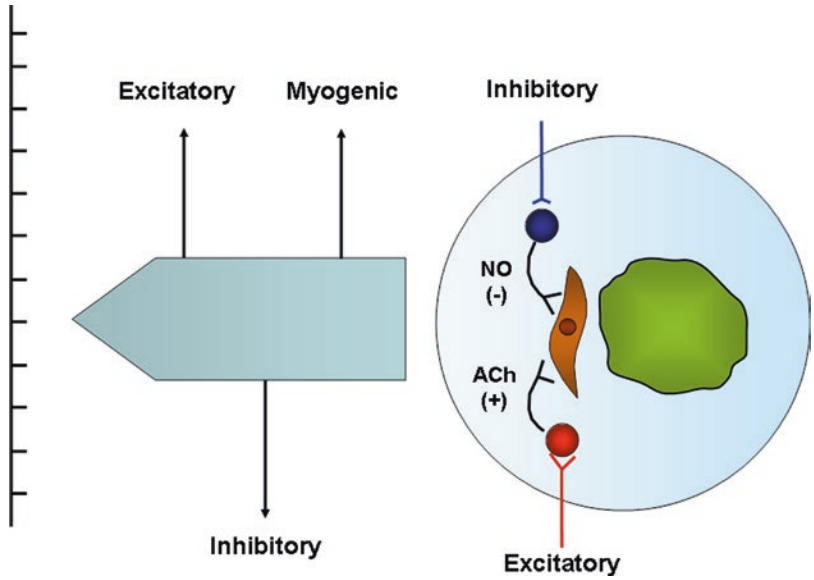

Fig. 68.2 Three mechanisms involved in the regulation of basal LES tone

Table 68.1 Factors affecting lower esophageal sphincter pressure

Factor	Increase LESP	Decrease LESP
Hormones	Gastrin, motilin, substance P, bombesin, galanin, pancreatic polypeptide, somatostatin	Secretin, CCK, glucagon, VIP, progesterone, calcitonin gene-related peptide (CGRP)
Neural agents	α-Adrenergic agonist, β-adrenergic antagonist, cholinergic agonist, serotonin	α-Adrenergic antagonist, β-adrenergic agonist, cholinergic antagonist, nitric oxide (NO)
Medications	Metoclopramide, domperidone, cisapride, histamine, prostaglandin F_{2a} erythromycin (motilin receptor agonist)	Nitrates, calcium channel blockers, theophylline, morphine, meperidine, diazepam, sildenafil, prostaglandin E_1, prostaglandin E_2
Food	Protein	Fat, chocolate, ethanol, peppermint

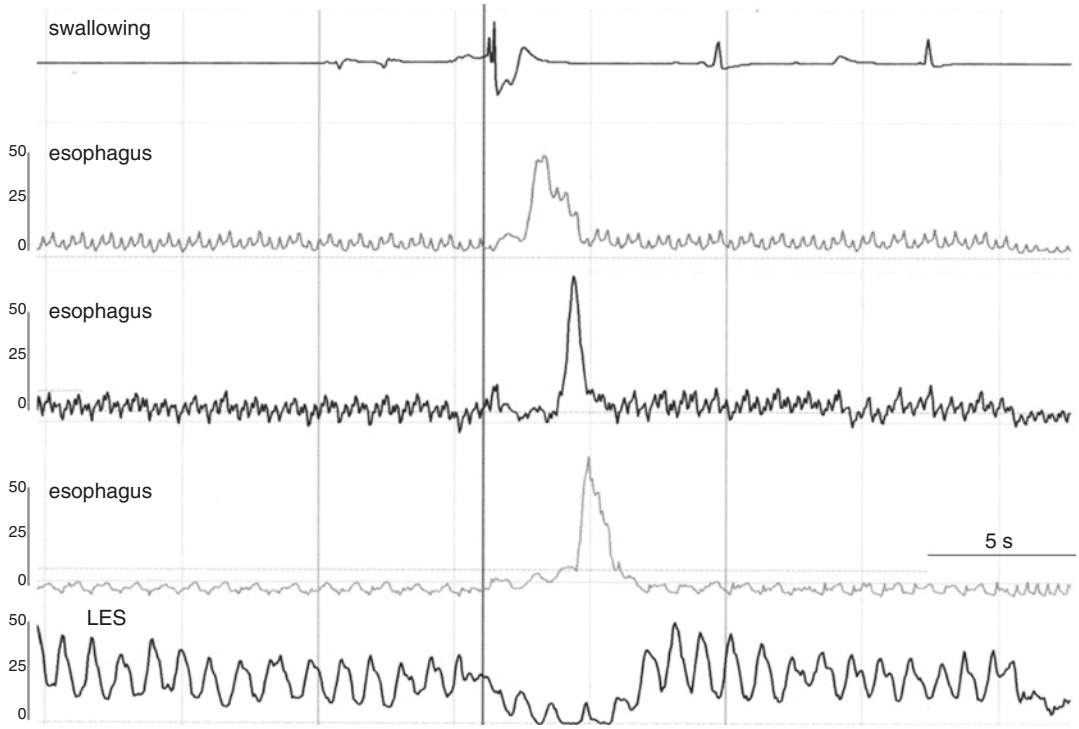

Fig. 68.3 Manometric recording of the esophageal peristalsis (second, third, and fourth channels) and relaxation of the lower esophageal sphincter (fifth channel). The first channel records the swallowing activity

proximal esophagus and lasts 5–10 s until the peristaltic wave reaches the distal esophagus. During relaxation, LES pressure falls to the level of gastric pressure. As the LES relaxes (an active process), it is passively opened by the bolus and propelled by the peristaltic wave. LES relaxation is followed by an after-contraction of the upper part of the sphincter, which likely represents the end of contraction wave as it reaches the distal esophagus [4]. Swallow-induced LES relaxation is part of primary peristalsis [1, 7, 8]. Central control is provided by preganglionic parasympathetic neurons originating in the nuclei of dorsal vagal complex, represented by the NTS, which receives sensory information from the pharynx and by the DMN, which contains preganglionic motor output to the LES [1, 7, 8]. Nitric oxide (NO) and acetylcholine are the principal neurotransmitters involved in the neural network at the DMN, even though γ-aminobutyric acid (GABA) is involved in the control of preganglionic neurons [12, 13]. The axons of preganglionic parasympathetic neurons

synapse with intramural inhibitory neurons. Convincing evidence supports the role of NO as the main postganglionic neurotransmitter mediating swallow-induced relaxation of the LES [13].

Transient relaxation of the LES refers to relaxation that is unrelated to either swallowing or secondary peristalsis. Transient LES relaxations (TLESRs) occur in healthy persons and represent the mechanism by which gas is vented from the stomach during belching [14]. Characteristically, they are associated with inhibition of the crural diaphragm [15]. TLESRs are of longer duration than swallow-induced relaxation of the LES, lasting between 10 and 45 s [16]. Manometric criteria for defining TLESR include: (1) the absence of a pharyngeal swallow for 4 s before and 2 s after the beginning of LES relaxation; (2) LES pressure falls of 1 mmHg/s; (3) $\leq$ 10 s to complete the relaxation of the LES; and (4) a nadir pressure during the relaxation $\leq$2 mmHg [16]. TLESRs are a neural reflex involving afferent and efferent pathways and a central pattern generator, corresponding to the nuclei of dorsal vagal complex [1, 8]. The afferent pathway is activated by stimulation of tension receptors in the proximal stomach, particularly the sub-cardial region, as well as by pharyngeal stimuli. Afferent neurons, through the vagus, travel to the NTS and the DMN via interneurons. The efferent pathway involves the same efferent neural pathways of swallow-induced LES relaxation. However, because the crural diaphragm is also inhibited during TLESRs, the phrenic nerve nucleus located in the spinal cord may also be involved [1]. TLESRs are more frequent in the seated position, with large meals, and in response to higher intragastric osmolarity. Although TLESRs are an essential component of belch reflex, they also represent the predominant mechanism underlying gastroesophageal reflux (GER) episodes in both normal and patients with GER disease (GERD). The proportion of reflux episodes attributable to TLESRs ranges between 100 % in children with nonerosive reflux disease (NERD) and healthy adults, compared to 60–80 % in children and adults with erosive esophagitis [17–20].

In children, LES pressure ranges between 10 and 40 mmHg [21, 22]. LES pressures of 5 mmHg above intragastric pressure are sufficient to maintain esophagogastric competence [1, 23]. Using a perfused side-hole pull-through technique, LES pressure was reported as very low in preterm infants, increasing from ~4 mmHg in premature infants younger than 29 weeks of age to 18 mmHg in term infants [24, 25]. By employing a micromanometric assembly with a sleeve device, LES pressure can be detected in preterm infants from 26 weeks of gestation [26]. In very premature infants, LES pressure ranges between 5 and 20 mmHg and promptly relaxes with swallowing, indicating full development of the central control of swallow-induced LES relaxation [27]. In addition, LES pressure in premature infants fluctuates substantially over time and significantly decreases after feeding. In both premature infants and term infants, TLESRs are the predominant mechanisms underlying GER episodes, indicating that the neural pathway responsible for transient inhibition of LES tone is already fully developed [26, 27]. Thus, LES motor patterns in premature infants are almost identical to those recorded in older children and adults.

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Gastroesophageal Junction: The Mucosa – Anatomy and Cell Types

69

Marta C. Cohen

Concept of GEJ

The gastroesophageal junction (GEJ) is anatomically defined by the proximal limit of the gastric folds. Histologically, it is characterized by the presence of a squamocolumnar junctional epithelium. In normal conditions, the anatomic GEJ also corresponds to the histologic transition between the esophageal squamous mucosa and the gastric mucinous columnar epithelium [5].

The squamocolumnar junction (Z line) is visible endoscopically and affords a key marker of the GEJ. To the naked eye, the Z line presents as a serrated line where small projections of red gastric epithelium converge with the whitish esophageal squamous mucosa (Fig. 69.1) [7]. The inlets of gastric mucosa are approximately 5 mm long and 3 mm wide, conferring the mucosa of the GEJ an irregular appearance, also known as ora serrata. Occasionally, the squamocolumnar junction of the GEJ may be straight. This most frequently occurs in the presence of a lower mucosal ring (Schatzki's ring) [7].

The mucosal GEJ usually lies within the lower esophageal sphincter and is found within 2 cm of the proximal edge of the gastric folds [7]. The distal esophagus may appear lined by columnar cells, also known as cardiac-type mucosa [11]. The term cardia is then equally used to refer to that part of the gastric mucosa that lies around the lower esophageal sphincter and to the columnar mucosa that can be found at the distal esophagus.

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Anatomy

The wall of the esophagus is described as constituted by four layers: mucosa, submucosa, muscularis propria, and serosa.

Cardiac Mucosa

There is great controversy regarding the nature and the origin of the cardiac-type mucosa at the GEJ. The view that the distal 2–3 cm of the esophagus is normally lined by columnar cardiac-type mucosa, extending between the esophageal squamous mucosa and the gastric acid-producing oxyntic mucosa, is denied by some investigators [4]. Chandrasoma et al. [4], in a retrospective and prospective autopsy study performed in pediatric and adult patients, demonstrated that columnar/cardiac mucosa was not identified in up to 70 % of the cases. These results are similar to an endoscopic study that reported the absence of cardiac mucosa in biopsies from the GEJ in 65 % of endoscopically normal patients [13]. These authors expressed the view that, even if present,

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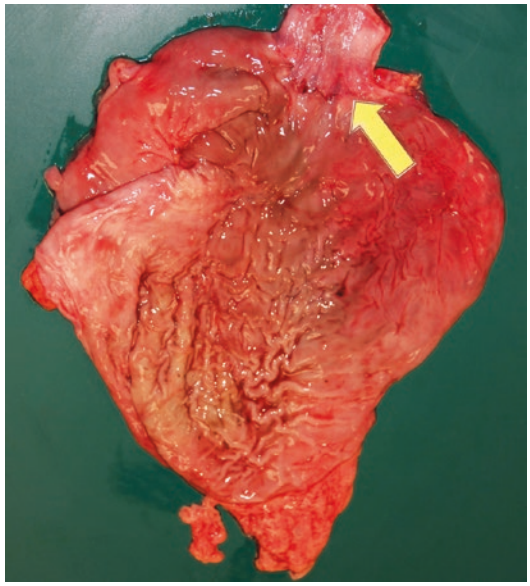

Fig. 69.1 Postmortem specimen from a 4-year-old child showing the irregular gastroesophageal junction (*arrow*) where the white esophageal mucosa joins the red gastric mucosa

cardiac mucosa and oxyntocardiac mucosa demonstrated considerable circumferential variation among individuals. They concluded that, when seen, the length of cardiac mucosa or oxyntocardiac mucosa in virtually all children is less than the 1–2 cm which is considered normal four decades ago [4, 11]. Moreover, the authors suggested that the presence of cardiac or oxyntocardiac mucosa represents early histological evidence of gastroesophageal reflux [4].

On the contrary, other investigators consider that cardiac mucosa is a normal structure at the GEJ and that it is defined by the presence of mucous cells without regard to the presence or absence of parietal cells (oxyntic mucosa) [14]. Cardiac mucosa was identified in all 33 autopsied children although with a usual length of less than 2 mm [14]. Another study conducted in fetal and pediatric postmortems concluded that cardiac mucosa contains both mucous and mixed glands, varies with age, is gastric (rather than esophageal) in origin, and does not develop before 13 weeks of gestational age [18]. More recently, a postmortem study performed in 253 unselected patients confirmed that cardiac mucosa was uniformly present adjacent to the squamous epithelium at the GEJ (either as pure cardiac mucosa or as oxyntocardiac mucosa), arguing against the hypothesis that cardiac mucosa is an acquired metaplastic lesion [16]. In our experience, columnar-lined cardiac-type mucosa is usually seen at the GEJ in fetuses (Fig. 69.2a) and children (Fig. 69.2b). Interestingly, the columnar cells of the cardiac-type mucosa present at the distal esophagus/GEJ region contain neutral mucins and can also contain acidic mucins [6, 16]. Both types of acidic mucins are more often present in the underlying glands (Fig. 69.2c).

As the cardiac mucosa narrows and changes with age [9, 10], it is likely that the older age of the patients studied by those who deny the existence of native cardiac mucosa in the upper stomach was a confounding factor [1–4, 8, 17]. Despite this debate, it has been suggested that it is still possible that a metaplastic expansion of the cardiac mucosa into the distal esophagus can occur as part of the stepwise transformation of the mucosa as a consequence of long-standing gastroesophageal reflux [6].

The Squamous Mucosa

The mucosa is composed of the lamina propria and the muscularis mucosae, both lined by epithelium. This is most usually non-keratinizing squamous epithelium (Fig. 69.3). As indicated above, in children, a short segment of the esophageal mucosa at the level of the GEJ can be lined by columnar (cardiac type) epithelium.

The non-keratinizing squamous epithelium is composed of three major cell layers: a deep basal cell layer, an intermediate or prickle cell layer, and a superficial functional cell layer.

The basal cell layer rests on the basement membrane and is the regenerative part of the mucosa. Basal cells are cuboidal and the layer is up to three cells deep or less than 15 % of the total mucosal thickness (Fig. 69.4). In comparison with the intermediate and superficial squamous cells of the mucosa, the basal cells appear smaller and darker. This is because their shape is cuboidal rather than polygonal, and they contain less

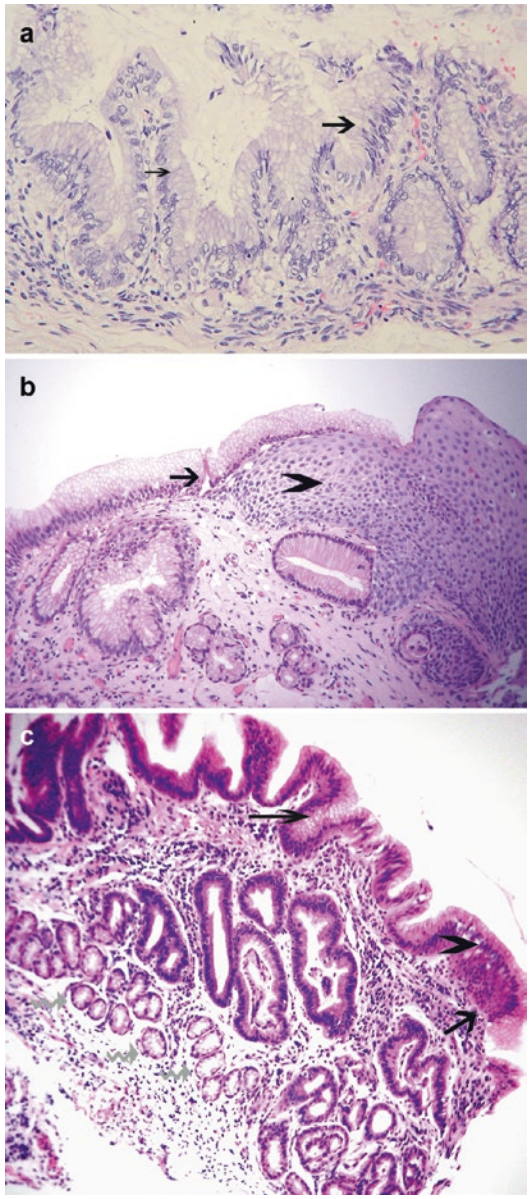

Fig. 69.2 Columnar cardiac-type mucosa is usually present at the gastroesophageal junction in fetuses (**a**, hematoxylin and eosin stain × 20) and children (**b**, hematoxylin and eosin × 20). Note in (**b**) how the squamous non-keratinizing epithelium (*arrow head*) is in direct contact with the columnar cardiac-type mucosa (*arrow*). Mucous-secreting glands are seen in the lamina propria (**c**, *curved arrow*) present below the columnar epithelium (*straight arrow*)

glycogen compared with the more superficial squamous cells. In the distal esophagus, and at the GEJ, it is not uncommon that the basal cell

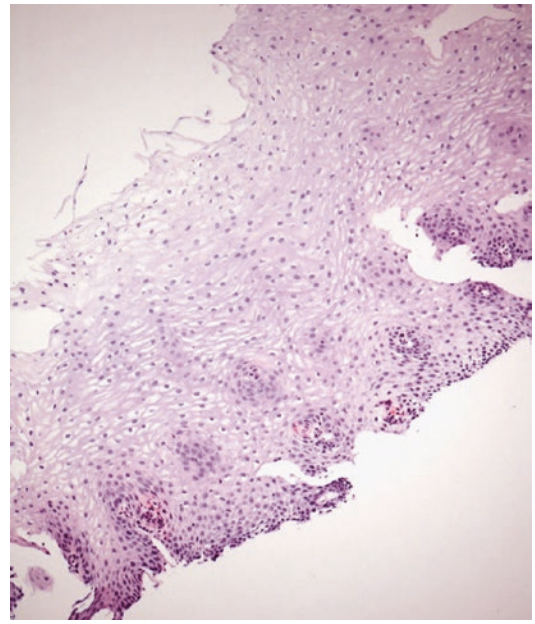

Fig. 69.3 Most of the esophageal mucosa is lined by non-keratinizing squamous epithelium (hematoxylin and eosin stain × 10)

layer is thickened and the papillae appear elongated and increase in number (Fig. 69.5). In cases of gastroesophageal reflux, the basal cell layer of the mucosa proliferates as a response to the increased turnover of the epithelium and becomes hyperplastic (it contains more than three cells in thickness) [7].

The intermediate or prickle cell layer is composed of several layers of polygonal cells with numerous intercellular bridges [12]. The superficial functional layer contains pale cells, rich in glycogen, gradually flattened, and with pyknotic nuclei. In addition, their long axis gradually becomes parallel to the basal membrane (Fig. 69.4).

T-cell lymphocytes are seen in an intraepithelial location. In normal patients, they are less than 6/high-power field [15]. Most of these lymphocytes have a cytotoxic immunoprofile (CD3+ and CD8+) [12] and are usually seen above the basal cell layer [7]. They "squeeze" between epithelial cells, making their nuclei to adopt an angulated shape, responsible for the name "squiggle" or "wiggly" cells, to which they are sometimes referred [12].

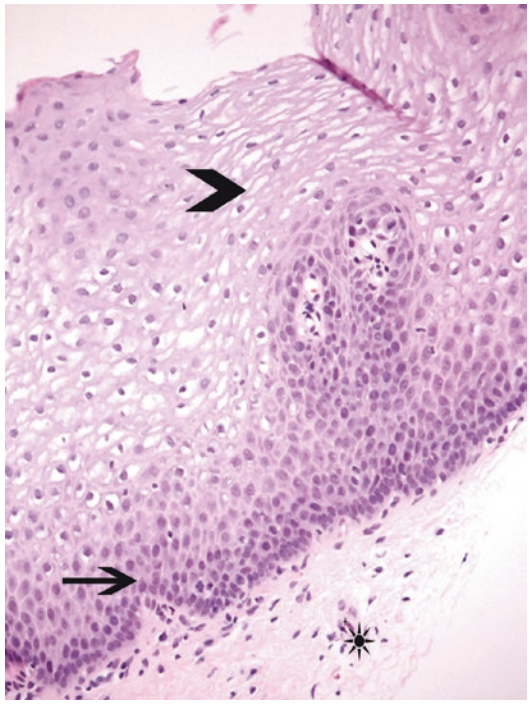

Fig. 69.4 The squamous non-keratinizing epithelium lining the esophageal mucosa is composed by a deep basal cell layer (*arrow*), an intermediate layer, and a superficial functional cell layers (*arrow head*). The epithelium lies above the lamina propria (*star*) (hematoxylin and eosin × 20)

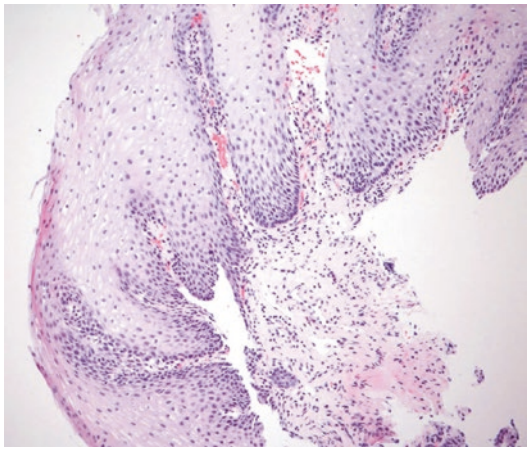

Fig. 69.5 At the distal esophagus, the basal cell layer is normally thickened, and the papillae appear elongated and increased in number (hematoxylin and eosin × 10)

Other cells present in the mucosa include endocrine cells, rare melanocytes, and Langerhans cells. The latter is part of the local immune system and acts as antigen-presenting cells. Occasionally mast cells and single eosinophils can be found in the epithelium of the normal GEJ [12].

The normal mucosa has innate mechanisms of resistance against reflux. Several factors contribute to the resistance of the epithelium against regurgitated gastric contents [12]: the epithelial integrity maintained by the processes of cell proliferation, differentiation and regeneration; the small amount of mucus that normally covers the luminal side of the mucosa; the acidic muco-substances present in the intercellular spaces of the intermediate and superficial layers of the non-keratinizing squamous mucosa; the cell junctions that provide protection against the penetration of toxic substances; the immune response provided by intraepithelial T lymphocytes and antigen-presenting Langerhans cells: and the presence of stromal papillae which contain capillary blood vessels that provide nutritional support among other benefits to the epithelial cells.

The Lamina Propria

This is comprised of loose connective tissue located between the muscularis mucosae and the epithelium (Fig. 69.4). It contains vessels and mucus-secreting glands. The local immune system is represented by a few T lymphocytes of CD4 (helper) and CD8 (cytotoxic) phenotype, alongside IgA-secreting plasma cells [7]. The connective tissue projects into the overlying epithelium as papillae. These contain delicate blood vessels that nourish the mucosa. In normal conditions, the papillae do not reach the upper third of the epithelium. However, in circumstances of gastroesophageal reflux, they become hyperplastic, reaching the most superficial part of the squamous mucosa. These features can be seen in normal patients at the very distal end of the esophagus.

The glands present in the lamina propria of the GEJ are mucous-secreting cardiac-type glands.

The Muscularis Mucosae

It is composed of longitudinal-oriented smooth muscle fibers and is characteristically thicker at the distal esophagus (GEJ) than in other segments of the esophagus.

The Submucosa

This is composed of connective tissue containing blood vessels, nerves, and mucus-secreting glands. These glands have a lobulated shape, produce acid mucins, and drain to the surface of the esophagus by squamous-lined ducts.

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Epidemiology of Gastroesophageal Reflux Disease

70

Michael A. Manfredi

Introduction

In preparing to write a chapter on the epidemiology of infant and childhood gastroesophageal reflux (GER), it becomes quite apparent that many more questions arise than answers. In a large part, this is due to the lack of standard definitions, the variability in the tests used to diagnose GER, and the absence of large population-based and multicenter trials. Therefore, the true prevalence of GER in children is in fact unknown. In this chapter, we will discuss what is known about the epidemiology of pediatric GER as well as define the areas that need further research and investigation.

GER is one of the most common gastrointestinal disorders in adults. It has been reported that 10–20 % of adults in the Western population have weekly symptoms defined by at least weekly heartburn and/or acid regurgitation [1]. In Asia the prevalence is lower at less 5 %. The pediatric literature has lacked the multicenter trials necessary to capture the true prevalence of GER.

The Pediatric Health Information Survey (PHIS) database is a data collection system for 28 pediatric hospitals across the United States developed in order to assess the length of hospital stay and charges associated with different pediatric diseases. Gibbons et al. retrospectively reviewed the PHIS database for gastroesophageal reflux disease (GERD) from 1995 to 2000, which encompassed 1.8 million discharges. GERD represented approximately 4 % of all pediatric hospital admissions annually, and admissions for GERD have been increasing significantly during the past 5 years, the highest rate being in the 12- to 24-month age group, with a male predominance for all ages [2].

A cohort study in the United Kingdom was performed using data extracted from The Health Improvement Network (THIN), which is a primary care medical research database containing systematically recorded anonymous records for participating primary care practices [3]. There were approximately 2.3 million patients at the time of the study, which is approximately 4 % of the total UK population. In the study years of 2000–2005, a total of 1700 children and adolescents were recorded with a first diagnosis of GERD. The incidence of GERD was 0.84 per 1000 person-years. Further stratifying the incidence by age, we see that the incidence of GERD for 1-year-old children was 1.48 per 1000 person-years. Incidence then decreased until the age of 12 years, but increased after this age to a maximum at age 16–17 years of 2.26 per 1000 person-years for girls and 1.75 per 1000 person-years for boys. The annual prevalence of GER in 2003 was 1.05 % with an overall prevalence during the whole study period of 1.25 %. This and the previous study were both limited since they were both

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retrospective and they relied on billing and/or diagnosis codes. These codes do not rely on standardized definition of GER so the accuracy of the diagnosis is questionable.

GER Definitions

The first attempt at defining and characterizing GER in infants was the Rome II criteria [4]. Regurgitation is the involuntary return of previously swallowed food or secretions into or out of the mouth. This article also gave criteria for infant regurgitation which include (1) regurgitation two or more times per day for 3 or more weeks. (2) There is no retching, hematemesis, aspiration, apnea, failure to thrive, or abnormal posturing. (3) The infant must be 1–12 months of age and otherwise healthy. (4) There is no evidence of metabolic, gastrointestinal, or central nervous system disease to explain the symptom (see Table 70.1). Rome II, however, did not define or give criteria for childhood GER.

Recently an international group of pediatric gastroenterologists using a modified Delphi technique came up with consensus statements on the definition of gastroesophageal reflux disease (GERD) in the pediatric population [5]. This was developed in a similar way to the Montreal definition of gastroesophageal reflux in adults. Through this process, regurgitation in pediatrics is defined as the passage of refluxed contents into the pharynx or mouth or from the mouth. GERD is defined as the reflux of gastric contents that causes troublesome symptoms and/or complications. The definition of GERD is complicated by unreliable reporting of symptoms in children less than 8 years of age. Regurgitation is a characteristic symptom of reflux in infants, but is neither necessary nor sufficient for a diagnosis of GERD, because it is not sensitive or specific. The Delphi technique was a rigorous process with the intended use of developing new clinical practice guidelines as well as standardizing future pediatric population-based studies of reflux symptoms.

Table 70.1 Rome II criteria for infant regurgitation

Diagnostic criteria
1. Regurgitation two or more times per day for 3 or more weeks
2. There is no retching, hematemesis, aspiration, apnea, failure to thrive, or abnormal posturing
3. The infant must be 1–12 months of age and otherwise healthy
4. There is no evidence of metabolic, gastrointestinal, or central nervous system disease to explain the symptom

Prevalence of GER in Infants

Much of the prevalence data for infant GER comes from a single study that surveyed 948 infants from 19 pediatric practices in the Midwestern United States [6]. Regurgitation of at least one episode a day was reported in half of 0–3 months old. This symptom decreased to 5 % at 10–12 months of age ($p < 0.001$). The peak reported regurgitation was 67 % at 4 months; the prevalence of symptoms decreased dramatically from 61 to 21 % between 6 and 7 months of age. Peak regurgitation reported as a "problem" by parents was most often seen at 6 months (23 %); this prevalence decreased to 14 % at 7 months of age. Since Nelson and colleagues' initial prevalence study, there have been several other studies looking at the prevalence of infant GER. Martin et al. looked at a large Australian infant cohort ($n = 1981$) and found of peak prevalence of GE reflux of 41 % between 3 and 4 months of age and thereafter declined to <5 % between 13 and 14 months of age [7]. Campanozzi et al. prospectively followed an Italian cohort of 2642 patients aged 0–12 months [8]. Unlike the previous two studies, this study used a standard agreed upon definition of GER. They used the Rome II definition for GER and found that 313 infants (12 %) had GER. This study also followed these children over 2 years and found that GER resolved in 27 % by 6 months and 61 % at 1 year of age.

Prevalence studies looking at GER in different ethnic populations have also been performed. Miyazawa et al. looked at a cohort of 921 Japanese infants and found that 47.1 % had one or more regurgitation or vomiting episode per day at 1 month [9]. This proportion decreased to

28.8 % at 4 months old and 6.4 % at 7 months old. There was no significant difference in the prevalence of regurgitation or vomiting between breast-fed infants and formula-fed or mixed-feeding infants. Osatakul et al. looked at a cohort of 145 Thai infants in a 1-year study. The prevalence of reflux regurgitation peaked at 2 months at 86.9 % and significantly decreased to 69.7 % at 4 months, 45.5 % at 6 months, and 22.8 % at 8 months [10]. At 1 year of age, only 7.6 % of infants had reflux regurgitation, and again there was no significant difference in prevalence of reflux regurgitation between breast-fed and bottle-fed infants. We therefore see that GER in infancy is common and a majority of symptoms resolve within the first year of life; however, there are variations in reported prevalence that may be related to ethnicities or due to the definition of GER used in the study.

Prevalence of GER in Childhood

Nelson et al. in another cross-sectional survey of Midwest pediatric practices examined the prevalence of GER symptoms in children [11]. The parents of 566 children aged 3–9 were surveyed and reported symptoms of heartburn (1.8 %), epigastric pain (7.2 %), and regurgitation (2.3 %). In addition 615 children with an age range of 10–17 were surveyed. The prevalence of heartburn, epigastric pain, and regurgitation was 5.2 %, 5.0 %, and 8.2 %, respectively.

Prevalence of GER Complication in Children

The prevalence of GER complications in children is also not well described. El-Serag et al. retrospectively reviewed 402 children who underwent upper endoscopy with the diagnosis of GER. In this study one third of these patients had endoscopic evidence of erosive esophagitis [12]. Another complication of GER is Barrett's esophagus. In adult population studies, it appears that Barrett's is uncommon in the general population with an incidence of 1.3–1.6 % [13]. The prevalence of Barrett's esophagus in children is not well characterized. In the El-Serag study, they suspected Barrett's in 2.7 % of patients; however, there was no histological evidence in those same patients [12]. The Pediatric Health Information System database suggested that the prevalence of Barrett's rose from less than 2 % in 1997 to 3.8 % in the first 6 months of 2000; however, since this is based on coding data, the accuracy of this data is questionable [14].

Prevalence of GER in Special Pediatric Populations

Prematurity

GER is a common finding in premature infants. It has been reported that that GER occurs on average three to five times per hour in premature babies [15]. There have been single-center studies showing more that 85 % or premature infants have GER proven by pH monitoring [2]. This common clinical diagnosis has been associated with longer NICU stays and higher hospital costs [16, 17]. When the promotility medication cisapride was on the market, a study showed that 19 % of premature infants admitted to teaching hospitals in the United States received this medication [18]. A retrospective study of extremely low birth infants from the National Institute of Child Health and Human Development (NICHD) network centers showed that 25 % of infants were discharged home on medications for GER [19].

Like in infant and childhood reflux, there is considerable variability between NICU units for diagnosing and managing GER. Dhillon et al. demonstrated that the diagnosis of GER was extremely heterogeneous in 77 neonatal intensive care units in the United Kingdom [20]. In this study, GER was diagnosed based solely on clinical grounds in 42 % of units; despite the availability of pH monitoring in 93 % of units, it was only used in 32 % of suspected GER patients. Another study by neonatologists, gastroenterologists, and pulmonologists surveyed on the symptoms, treatment, and diagnosis of GER in premature infants. This study revealed a near-complete disagreement between specialists [21].

Neurologically Impaired

The prevalence of GER has been well reported in neurologically impaired children. There is a wide reported incidence range from 15 to 75 % which could be attributed to small patient numbers studied and variations in GER testing [22]. In the THIN cohort study done in the United Kingdom, children with neurodevelopment disabilities, such as cerebral palsy, motor neuron disorders, and other neurological impairments, had a greater than threefold increase in the risk of a GER diagnosis. Of the 107 children with neurological impairment with a GER diagnosis, 26 % received the diagnosis of esophagitis [3].

The proposed mechanisms for this include prolonged supine positioning, scoliosis, hiatus hernia, and CNS dysfunction leading to poor lower esophageal sphincter function. Bohmer et al. looked at 69 neurologically impaired children with symptoms of GER (vomiting, regurgitation, food refusal, hematemesis, and behavioral problems) and who underwent endoscopy. Fifty-two children were found to have esophagitis on endoscopy. In this same study, there was marked improvement of persistent vomiting, regurgitation, food refusal, iron deficiency anemia, and signs of depression at the end of treatment [23]. The high prevalence of GER in the neurologically impaired population warrants close monitoring of GER symptoms and treatment with acid-blocking medicine [23].

Asthma

It has been hypothesized that asthma symptoms are caused by the reflux of stomach contents reaching the respiratory tract or via stimulation of the esophagobronchial reflex. Alternatively, symptoms such as cough and wheezing may cause reflux through an increase in intra-abdominal pressure. The relationship between GER and asthma in children is another area that has deficiencies. These range from small sample sizes, lack of standardized definitions for reflux and asthma, as well as different definitions used for abnormal test values. In two systematic literature reviews, the estimates on the prevalence of GER in children with asthma varied between 19.3 and 65 % and 19.3 and 80 %, giving a pooled sample-size-weighted average prevalence of 23.4 % in one study and 22.8 % in the other [24, 25]. The variation in the results is likely secondary to the methodology used to identify GER. The studies using an esophageal pH probe reported relatively high prevalence estimates (33–65 %), whereas the studies that used a questionnaire to assess GER symptoms reported the lowest prevalence estimates (19.3 and 19.7 %) [25].

The relationship between asthma and GER in adult studies is clearer. A systematic review of the adult literature reported a significant association between GERD and asthma in adults; however, a temporal relationship could not be established [26]. In the published systematic reviews in pediatrics, the data suggest a possible association, but further well-constructed studies are needed.

Natural History of GER or Do Children with Reflux Grow Up to Be Adults with Reflux?

Like the prevalence of GER in children, little is known definitively on the natural history of GER. There is debate in the literature regarding whether infants and children outgrow reflux or they are a high-risk population for becoming adults with GER. Nelson et al. who prospectively looked at her original cohort of infants and surveyed them 1 year later. Based on GER questionnaires, Nelson reported that infants with GER symptoms at 6 and 12 months of age outgrew it within 1 year [27]. Campanozzi et al.'s prospective GER study on an Italian infant cohort showed that all 210 subjects were followed longitudinally over a 2-year period and reported a complete resolution of GER symptoms by the end of the 24-month period [8]. Both of these studies support the idea that infants will outgrow reflux.

There is also growing literature that supports the idea that GER in childhood is a more chronic disease. El-Serag et al. followed up young adults 10 years post their diagnosis of GERD. A total of

113 cases completed the questionnaires, and at least weekly heartburn or regurgitation was reported in 52 (46 %) participants, 94 % of whom were taking proton pump inhibitors, H2RA, or antacids. This study suggested that GER can persist from childhood to young adulthood [28]. Another study surveyed 400 adults, 225 of whom were classified as refluxers, 154 non-refluxers, and 21 claimed to not know their reflux status, and the majority (63 %) of refluxers recalled at least one childhood GER symptom, compared to 35 % of the non-refluxers ($p<0.001$) [14]. Although this study has recall bias, it suggests that GER is a chronic disease. Martin et al. in a cohort study of Australian infants made the observation that children with over 90 days of GER during the first 2 years of life were more likely to have GER symptoms at 9 years of age. Children with frequent infant spilling, compared with those with no spilling, had a relative risk of 2.3 (95 % confidence interval: 1.3–4.0) of one or more GER symptoms at 9 years of age: a relative risk of 4.6 (95 % CI: 1.5–13.8) for heartburn, 2.7 (95 % CI: 1.4–5.5) for vomiting, and 4.7 (95 % CI: 1.6–14.0) for acid regurgitation [7].

Two important studies emphasize the important need to better understand the natural history of GER. The first was Lieberman et al. who reported the prevalence of Barrett's esophagus being strongly associated with duration of GER symptoms [29]. This was an observational, prospective, community-based study that demonstrated an odds ratio of 6.4 in patients with symptoms for more than 10 years ($p<0.001$). The second study was by Lagergren et al. who first demonstrated a strong and probably causal relation between GER and esophageal adenocarcinoma. This study was a case-controlled population-based study done in Sweden [30]. The risk of esophageal adenocarcinoma also increased with an increasing duration of symptoms. The adjusted odds ratio for esophageal adenocarcinoma was 43.5 (95 % confidence interval, 18.3–103.5) among persons with both long-standing symptoms and severe symptoms when compared with asymptomatic persons [30]. These two studies stress the need for well-designed, population-based epidemiologic studies to accurately assess pediatric GER and identify children at risk for chronic GER.

Future Directions

In order to further research in the epidemiology of pediatric GER, validated and standardized age-appropriate definitions are needed to critically and reliably assess data. This process has already started with the Montreal definitions for pediatric GER [5]. There is a need for uniformly accepted, reproducible, and validated symptom-scoring instrument, quality of life index, as well as a pediatric GERD severity indexes to assess disease throughout the study. These tools should be made for both parents and children. Multicenter longitudinal and cross-sectional studies with pediatric and family cohorts are needed to study incidence, prevalence, and natural history of GER. Only then will investigators be able to determine risk factors for the development of chronic GER, GERD, Barrett's esophagus, and esophageal adenocarcinoma.

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The Genetics of GER and GERD

71

Isabel Filges and Raoul I. Furlano

Introduction

We have learned much more about the molecular genetics of diseases in the last few years than in the previous decades. This includes both a new appreciation for the role of rare genetics variation and the identification of the first contributory common variants by genome-wide association. These data show that although the population attributable risk of common variation may be moderate to large, the genotype risk of common variants at the individual level is small. In contrast a large number of diverse rare mutations of large effect have been identified, but none appear to be specific to GERD. All of these findings point to extreme genetics heterogeneity suggesting complex gene-gene or gene-environment interactions in GERD etiology. Available knowledge, reviewed below, also suggests that phenotypic presentation is the result of complex interactions and diverse pathogenetic mechanisms.

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Background

Gastroesophageal reflux (GER) is the passage of gastric contents into the esophagus with or without regurgitation or vomiting and is a normal physiologic process occurring several times per day in infants, children, and adults [35, 50, 59]. In contrast, alterations in several protective mechanisms including hiatal hernia allow physiologic reflux to become gastroesophageal reflux disease (GERD) [34].

The diagnosis of GERD is mainly clinical when the reflux of gastric contents causes troublesome symptoms and/or complications [52]. However, the spectrum of clinical symptoms is large and variable, differing between infants, children, and adults. Clinical diagnosis is challenging as in infants and toddlers, there is no symptom or symptom complex that is diagnostic of GERD or predicts response to therapy. Esophageal pH impedance monitoring [49], manometric studies, endoscopy and biopsy, and barium contrast radiography can help in the diagnosis of GERD or its underlying causes as well as in the differentiation to other pathologies. In elderly children or adults, heartburn is often the leading clinical presentation.

The risk of Barrett's metaplasia is considered as a complication of chronic GERD. This premalignant lesion of the esophageal mucosa is correlated with the development of adenocarcinoma of the esophagus, which has increased in incidence over the past 20 years faster than any other form of cancer.

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Despite clinical heterogeneity, proper diagnosis should be a clinical goal and is not only essential to the management of patients with GERD but is a prerequisite for inclusion of patients in studies aiming at the identification of its genetic origin. Given the variety of presenting symptoms and the lack of a noninvasive gold standard, the inaccurate diagnosis of GER and GERD can present a major pitfall in genetic studies.

However, significant familial clusterings of reflux symptoms, hiatal hernia, erosive esophagitis, Barrett esophagus, and esophageal adenocarcinoma suggest some heritability of GERD and its complications. Differences between adult and pediatric GERD may lead to caution in extrapolating data from one to another. However, as a genetic basis has been considered in the literature for both ends of the age spectrum recently, it is worth reflecting on the literature as a whole. Nonetheless it may be distinct genetic predispositions identified for different presentations, including presentations in different age groups.

Besides GERD as an isolated disease, several other pediatric patient populations appear to be at higher risk for GERD than healthy infants, children, or adolescents. These include individuals with neurologic impairment, obesity, esophageal atresia, chronic lung diseases, those with a history of premature birth, and a number of genetic syndromes that we will specifically discuss in this chapter.

Twin Studies

Individuals within families share a similar environment and may experience similar diseases based on environmental influences only. When studying the genetic contribution to disease, confounding by environmental factors can be minimized by looking at twins and very young children. Twin studies have been proved to be a powerful methodology for studying the influence of nature (genes) and nurture (environment) on a particular phenotype. As monozygotic twins share virtually identical genetic material, phenotypes which have a genetic basis will be more highly correlated between twins that are monozygotic when compared with dizygotic twins.

Two large twin studies of familial GERD used 3,000 adult twin pairs from the Minnesota Twin Registry [59] and 8,401 adult twin pairs from the Swedish Twin Registry [11]. The former study found 19 % concordance for monozygotic versus 4 % for dizygotic pairs. The latter study compared concordance for reflux defined by heartburn or acid regurgitation occurring at least weekly in twins aged 55 or older, 15.3 % having reflux. They found 31 % concordance for monozygotic and approximately 13 % for dizygotic pairs. The limited concordance in both studies in the monozygotic pairs (19 % and 31 %, respectively) suggests markedly decreased penetrance or complex non-Mendelian factors as well as environmental influences participating in the origin of disease. Similarly, Mohammed et al. [38] performed a comparison of 4,480 twin pairs in the UK of the heritability of GERD. Again, GERD was defined as symptoms of heartburn or acid regurgitation at least once a week. A total of 1,960 twin pairs were evaluable, with a prevalence of GERD of 18 %. Case wise, concordance rates were significantly higher for monozygotic than dizygotic twins (42 % versus 26 %; $P < 0.001$). Their heritability estimate was that 43 % of the variance in liability to GERD is due to additive genetic factors.

Gene Identification

Approaches of gene identification in GERD are challenging as there are multiple phenotypes and the fundamental processes of disease origin are poorly understood and probably diverse. Successful identification of candidate genes is generally dependent on well-defined phenotypes, shared biological processes, or pathway interactions.

Linkage Studies

The number of linkage studies concerning GER and GERD is limited, and studies have shown

inconsistent results with regard to the identification of candidate loci. The Center for Genomic Sciences; Allegheny Singer Research Institute; the Pediatric/Adolescent Gastroesophageal Reflux Association (PAGER), founded in 1995 by children and parents who suffer from chronic severe GER; and the patient-supporting Fourth Love Foundation, specifically supporting GERD-related research efforts, collaborated on a genome-wide linkage study aiming to identify candidate loci for GER/GERD. By restriction of the phenotype to severe pediatric GER 20 families with multigenerational history of GERD were identified. Five families with 26 affected members had been identified through PAGER suggesting autosomal dominant inheritance with high penetrance and were selected for the study. A genetic locus on 13q14 was mapped cosegregating with the phenotype in families with multiple affected members [30]. Using polymorphic microsatellite markers, a gene for GERD was mapped to a 13 centimorgan (cM) region on chromosome 13q with a maximum multifamily multipoint LOD score of 7.15. Within the chromosomal region 13q14, the gene *HTR2A*, encoding for the 5-hydroxytryptamine receptor 2A, was an attractive candidate gene given the role of serotonin throughout the gastrointestinal tract. However, sequencing of the *HTR2A* gene and its promoter on affected and unaffected family members revealed benign polymorphisms but no mutations segregating with the disease phenotype. Additional linkage analysis narrowed the region to a 9cMorgan interval which did not include *HTR2A* [29]. Later the same group screened affected patients for exonic mutations of all genes within the linkage locus without concluding to causative mutations [28]. Linkage of GERD to 13q14 was inferred in a linkage study of five additional well-characterized families [41]. Differences in the findings of these two major linkage studies were proposed to lie in the age and phenotypic disparity between the subjects of the studies [40]. Whereas in the latter one the phenotype was defined as typical infantile GERD with esophagitis, Hu et al. excluded children whose GERD was limited to infancy [30]. Phenotypic variability, genetic heterogeneity of GERD itself, or both were discussed to explain the different study outcomes [40].

Asling et al. [3] performed whole genome linkage analysis in 36 families by identifying children diagnosed with GERD by an abnormal finding from endoscopic examination, a 24 h esophageal ph test, or having been subject for fundoplication and a positive family history. A region on chromosome 2, containing collagen type III alpha 1 (*COL3A1*), was identified (LOD = 3.3) in families with dominant transmission of GERD, stratified for hiatal hernia. *COL3A1* showed significant association with GERD in an independent pediatric trio cohort (p(corr) = 0.003). The association was male specific (p(corr) = 0.018). The *COL3A1* association was replicated in an independent adult case-control cohort (p(corr) = 0.022). Moreover, male-specific association to hiatal hernia (p(corr) = 0.019) was found for a single nucleotide polymorphism (SNP) not associated to GERD. Collagen type III protein was more abundant in esophageal biopsies from male patients ($p = 0.03$). The authors concluded that *COL3A1* is a disease-associated gene in both pediatric and adult GERD and is associated with hiatal hernia in adult males. As the GERD- and hiatal-hernia-associated alleles were different, the authors proposed that two separate mechanisms were leading to disease. However, the data potentially could point to a connective tissue component in the etiology of GERD. A number of *COL3A1* mutations are described to cause autosomal dominantly inherited Ehlers-Danlos syndrome type IV, a connective tissue disease characterized by the joint and dermal manifestations as in other forms of the syndrome but also by proneness to spontaneous rupture of bowel and large arteries. The observation of frequent GER/GERD in patients affected by Ehlers-Danlos syndrome is not reported in the medical literature.

Association Studies

Genome-wide association studies (GWAS) between common sequence variation and phenotypic variation were recently performed for a

large number of human phenotypes. Altogether over 200 GWAS studies each including several thousand patients have now been published accounting for the statistical association and subsequent validation between a considerable number of genomic regions defined by SNP variation and common complex traits. Due to the discovery of the common variation in human population, the development of technologies for large-scale genotyping and biostatistical methods and the collection of a very large number of well-phenotyped sample GWAS were successful in identifying low-risk alleles, but the current clinical utility of these findings remains very limited [10]. This implies that even if the SNP genotype for all the SNPs that impact the trait is known, the ability to predict the phenotype is poor. SNPs chosen in the studies are common variants based on the HapMap studies and not causal factors, so if the variance in traits is explained by rare SNPs, the correlation between the SNP markers that were used and these rare SNPs could be quite low. Even if methods of genome-wide association studies based on full sequence will be improved in the near future, the prediction of an individual's disease risk given only his or her genome sequence may never attain useful accuracy apart from Mendelian disorders, especially if environmental factors or complex gene-environmental interactions mainly contribute to the disorder. However, even if the associated SNP does not accurately predict common traits, a newly defined locus might highlight molecular pathways involved in pathophysiological processes [20, 27, 55].

There are no large GWAS performed for GER or GERD probably due to the fact that very large patient cohorts with a stringent phenotype are needed to determine a risk allele.

However, de Vries et al. [18] suggest that enhanced perception of reflux events occurs in GERD as a consequence of increased sensory signal transduction that is partly genetically determined. They present data from a medium-sized case-control study and test the association with a common polymorphism of the gene *GNß3* that encodes the ß3 subunit of the G-protein, key to secondary messenger function and thus signaling in the gut.

In total, 363 GERD patients, defined as having esophageal pH <4> or = 6 % of time and/or symptom index > or = 50 % or symptom association probability > or = 95 %, participated and were studies against 373 healthy controls free of gastrointestinal symptoms. Genotyping was performed by molecular beacon assay. The C825T genotype was more prevalent in GERD patients relative to healthy controls (adjusted odds ratio (OR) =1.43, 95 % CI 1.04–1.98). GERD patients sensitive to physiological amounts of reflux displayed a higher OR (1.59) as did GERD patients with a positive symptom association score (1.50). The strongest association was detected in patients without concomitant functional dyspepsia and/or irritable bowel symptoms (OR = 1.66). They concluded that GERD is associated with *GNß3* polymorphism C825T and may mediate an increased response to neurotransmitters. The authors suggested that enhanced perception of reflux events occurs in GERD as a consequence of the increased sensory signal transduction. However, patient sample size is very small although the characterization seems to be robust.

GERD-Correlated Phenotypes

In 1995, Carre published the first reports of familial clustering of hiatus hernia (HH) that he called "partial thoracic stomach." The use of x-ray as a definitive diagnostic tool for HH and GERD makes the studies difficult to interpret today due to different diagnostic standards. In a large group of children, he identified 31 families with multiple affected members [13]. He also described a three-generation family with eight individuals presenting with HH [14]. In an evaluation of 406 younger siblings of 465 probands with HH, Carre et al. identified GERD symptoms and suggestive symptoms in 15 %. HH was detected in 3 % of siblings tested by fluoroscopic examination arguing against familial inheritance. Several other anecdotic reports of familial HH clustering have been published [23, 52]. Later on, studies on familial manifestations of GERD have focused on Barrett's esophagus (BE). The tendency to develop Barrett's esophagus is itself

thought to be a heritable trait. As summarized by Romero and Locke [46], the reported familial clusterings comprise 88 individuals, of whom 28 % had BE and 42 % had esophagitis or heartburn. Further three families with six individuals having either BE or esophageal adenocarcinoma were described [44]. As these findings were suggesting a familial tendency in BE, the Mayo Clinic conducted a prospective study to evaluate the prevalence of reflux symptoms in the relatives of 122 probands with either reflux esophagitis, BE, or esophageal adenocarcinoma [45]. Currently the clinical implications of genetic studies are restricted to acknowledging that familial clustering with an inherited predisposition to developing BE does exist [54]. In addition to genetic influences including male gender, contributing factors such as obesity, smoking, and gender were identified. A potential role of the microbiome is also discussed [51].

Related Syndromes

The increased frequency and severity of GERD among infants and children with neurological impairment and developmental disorders is well documented ("syndromic GERD"). It is assumed that underlying pathological changes in the nervous system of patients with developmental disorders probably affect physiological and neurological features leading to associated anomalies of the gastrointestinal tract (GIT). Developmental defects within the enteric nervous system are also likely to be the cause of significant functional disorders. The GIT develops from the embryonic gut, an endodermally derived epithelium which is surrounded by cells of mesodermal origin. Cell signaling between these two layers appears to control the patterning and organogenesis and plays a critical role in coordinating GIT development. The enteric nervous system develops from the colonization of neural crest cells which migrate down the developing GIT [22, 24]. Vagal neural cells are thought to give rise to the majority of these neuroblasts. The normal development of the enteric neural system is complex, involving cascades of signaling molecules that determine proliferation, migration, differentiation, and survival of these enteric neuroblasts. Developmental defects within the enteric nervous system appear to be related either to defects in vagal cell migration or the development of the intermyenteric and submucosal plexuses.

Chromosome Anomalies

For many years, cytogenetic identification of rare chromosomal anomalies serves for the identification of disease-related regions and genes by correlating genotypes to phenotypes in patients with similar chromosomal aberrations.

The most frequent chromosomal anomaly is trisomy 21 causing Down's syndrome (DS) with approximately 1 in 800 live births worldwide. Up to 77 % of DS children have associated gastrointestinal abnormalities, which are either of structural or functional nature. The affection of the enteric nervous system in DS might not only concern the anatomy but also nerve function. This suggests that developmental disorders of the enteric nervous system are probably involved in the functional gastrointestinal disturbances encountered in patients with DS. However, the interaction between the central and enteric nervous system and gastrointestinal involvement is still poorly understood. Mechanisms and pathways in brain development during embryogenesis are probably interlinked with enteric development, but the precise underlying mechanisms have to be elucidated. Functional motor disturbances of the esophagus and colon may be congenital or acquired and are relatively frequent. These include esophageal dysmotility syndromes (e.g., achalasia, gastroesophageal reflux, dysphagia) as well as chronic constipation and Hirschsprung's disease (HSCR) (2–15 %) occurring in association with DS. The pathogenetic role of threefold dosage of chromosome 21 and its possible genome interactions in the etiology of developmental and functional anomalies remains undetermined.

GER is one of the most frequently encountered esophageal symptoms in DS and is, in addition, probably underreported because of its

general frequency. An increase in the number of associated complications has been reported in the study by Hillemeier et al. [26], who showed a 43 % occurrence of serious complications arising from GER in DS patients. Central nervous system disease and gastrointestinal disease necessitating surgery have been independently associated with a poorer developmental outcome [56].

As cytogenetically visible anomalies in standard conventional karyotyping encompass a large number of genes, clear involvement of a particular genomic region does not typically reveal individual molecules which may be contributory. Advances in technology by the development of fluorescence in situ hybridization in the 1980s and the recent introduction of array-comparative genomic hybridization in the clinical investigations of children with developmental disorders allowed to define structural anomalies at the submicroscopic level. The identification of these disorders has not only increased the number of patients with a now-defined origin of their developmental disease but has also contributed to more detailed observation of the natural course of disease within the groups of patients with the same chromosomal anomalies. There are a number of well-characterized microdeletion syndromes which appear to be associated more frequently with GER/GERD. Examples are the microdeletion syndrome 22q11 [19], 1p36 deletion [9], Wolf-Hirschhorn syndrome [6–8], 22q13.3 deletion syndrome [36], 16p13.3 deletions leading to the severer form of Rubinstein-Taybi syndrome [4, 5, 25, 48], and Williams-Beuren syndrome [12, 32, 33] as well as anecdotally reported rare structural chromosome anomalies [16]. All of the described syndromes lead to neurodevelopmental impairment supporting the assumption that a developmental pathogenetic process in the enteric system may contribute to the origin of GER/GERD. As symptoms are not confined to children with a particular chromosomal anomaly, but also can be observed in a variety of microdeletion syndromes throughout the genome, genetic heterogeneity and possible complex underlying pathogenetic mechanisms in GER/GERD seem likely. The application of array-comparative genomic hybridization in clinical routine diagnosis of patients with developmental disorders will further contribute to the identification of additional patients as well as new distinct microdeletion syndromes.

Monogenic Disorders

To date, more than 4,500 single genes are known to cause a disease by Mendelian inheritance. A number of developmental syndromes as well as monogenic neurological disorders present with esophageal reflux as an adjunct symptom (Table 71.1).

Cornelia de Lange syndrome (CdLS) has been particularly studied for GER probably because symptoms in affected patients seem to be particularly severe. The Cornelia de Lange syndrome is caused by mutations in the *NIPBL* gene, which encodes a component of the cohesin complex, in about half of the clinically diagnosed patients [39]. An X-linked form of the disorder (CdLS2) can be caused by mutations in the *SMC1L1* gene, and a mild variant of Cornelia de Lange syndrome (CdLS3) has been related to mutations in the *SMC3* gene. Both genes encode different components of the cohesin complex. CdLS is recognized on the basis of characteristic facies (low anterior hairline, synophrys, anteverted nares, maxillary pragmatism, long philtrum, "carp" mouth) in association with prenatal and postnatal growth retardation, intellectual disability, and, in many cases, upper limb anomalies [57]. Gastroesophageal dysfunction in patients with CdLS was emphasized in medical literature, and gastroesophageal reflux with reflux esophagitis, aspiration pneumonia, and esophageal stenosis has been described [15, 35, 47]. Sommer et al. [53] examined 17 CdLS patients, ranging in age from 9 months to 19 years, and found that 13 had evidence of gastroesophageal reflux causing paroxysmal dystonic posture including torticollis and opisthotonus. A number of children with typical CdLS and congenital diaphragmatic hernia were reported [17, 21, 31]. In a series of 43 patients with CdLS, the incidence of GER and the correlation between its presence and severity and the clinical phenotype were evaluated [37]. Pathologic GER was evident in 28 (65 %) of the

Table 71.1 Monogenic disorders referenced in OMIM (Online Mendelian Inheritance in Man, www.ncbi.nlm.nih.gov/omim) for which gastroesophageal reflux is mentioned in the clinical synopsis

Syndrome/disease name	OMIM ID	Gene	Gene locus
Cornelia de Lange syndrome	#122470 #300590	*NIPBL* *SMC1L1* *SMC3*	5p13.1 Xp11.22 10q25.2
Rett syndrome	#312750, #300673	*MECP2* *CDKL5*	Xq28 Xp22.13
Lubs X-linked mental retardation syndrome (MRXSL)	#300260	*MECP2*	Xq28
Alpha-thalassemia/mental retardation syndrome (ATRX syndrome)	#301040	*ATRX*	Xq21.1
Opitz-Kaveggia syndrome	#305450	*MED12*	Xq13
Opitz GBBB syndrome	#300000 #145410	*MID1* Unknown	Xp22.2 22q11.2
Rubinstein-Taybi syndrome	#180849	*CREBBP*	16p13.3
Cohen syndrome	#216550	*COH1 (VPS13B)*	8q22
Kleefstra syndrome	#610253	*EHMT1*	9q34.3
Noonan syndrome	#163950	*PTPN11*	12q24.13
Cardiofaciocutaneous syndrome	#115150	*KRAS* *BRAF* *MEK1* *MEK2*	12p12.1 7q34 15q22.31 19p13.3
Costello syndrome	#218040	*HRAS*	11p15.5
C-like syndrome (Bohring-Opitz syndrome)	#605039	*CD96*	3q13.13q13.2
Dubowitz syndrome	%223370	Unknown	
Townes-Brocks syndrome	#107480.	*SALL1*	16q12.1
Osteopathia striata with cranial sclerosis (OSCS)	#300373	*WTX*	Xq11.1
Achondroplasia	#100800	*FGFR3*	4p16.3
Marfan syndrome	#154700	*FBN1*	15q21.1
Shprintzen-Goldberg craniosynostosis syndrome	#182212	*FBN1*	15q21.1
Cutis laxa type IIB (ARCL2B)	#612940	*PYCR1*	17q25.3
3-Alpha methylcrotonyl-CoA carboxylase 1 deficiency	#210200	*MCCC1*	3q27.1
Methylmalonyl-CoA epimerase deficiency	#251120	*MCEE*	2p13.3
Aromatic L-amino acid decarboxylase deficiency	#608643	*AADC*	7p12.2
Hypertrophic neuropathy of Dejerine-Sottas	#145900	*MPZ* *PMP22* *PRX* *EGR2*	17p11.2 1q22 19q13.2 10q21.2
Charcot-Marie-Tooth disease, demyelinating, type 1A (CMT1A)	#118220	*PMP22*	17p11.2
Charcot-Marie-Tooth disease, axonal, type 2B (CMT2B)	#600882	*RAB7*	3q21
Neuropathy, hereditary sensory, and autonomic, type IIA (HSAN2A)	#201300	*WNK1*	12p13.33
Neuropathy, hereditary sensory, and autonomic, type III (HSAN3)	#223900	*IKBKAP*	9q31.3
Neuropathy, hereditary sensory, and autonomic, type I, with cough and gastroesophageal reflux	%608088	Unknown	
Spastic paraplegia 9 (SPG9)	601162	*ALDH18A1*	10q24.1
Spinocerebellar ataxia 3	301790	Unknown	

43 patients. The incidence was not significantly different in patients with classic (93.3 %) versus mild (82.3 %) phenotype, whereas a strong correlation was present between the degree of esophageal damage and the clinical phenotype. Hyperactivity was the most frequent sign associated with GER, present in 23 (85 %) of the 28 patients.

There is a variety of other monogenic developmental disorders which present with symptoms of GER/GERD such as Rett syndrome, Ras-pathway-associated syndromes such as Noonan-Cardiofaciocutaneous and Costello syndrome, Kleefstra syndrome, and Cohen syndrome.

Interestingly the group of neuropathies, such as Charcot-Marie-Tooth CMT1A and 2B [1], and hereditary sensory and autonomic neuropathies are mentioned in association with GER, as well as spastic paraplegia [42]. Descriptions of patients with connective tissue diseases, especially fibrillinopathies, such as Marfan syndrome [43] and congenital contractural arachnodactyly [57] presenting with GER, remain rather rare and anecdotic.

Occurrence of GER/GERD in monogenic disorders seems to be widespread; however it seems to be mentioned in particular in neurodevelopmental and neurologic phenotypes. Whether this underlines a contribution of disturbance in enteric neurological mechanisms remains to be verified.

Closing Remarks

GER/GERD is a heterogeneous and probably complex disease with evidence for genetic but also environmental contribution to its origin first suggested on the basis of twin studies. The straightforward identification of genes or susceptibility genes seems to be particularly challenging as the clinical presentation and definition is highly variable and thus the borders between physiologic GER and definite GERD might be blurred. GER/GERD is a generally common finding, and its prevalence especially when associated with severe disabling disorders may be even underreported and the specific GER/GERD phenotype only marginally mentioned. The pathogenesis of GERD in regard to cellular mechanisms remains sparsely elucidated, but there are lessons learned from chromosomal and monogenic diseases suggesting a major contribution of disturbance in the enteric nervous system to the pathogenesis. Despite the efforts made in the identification of low-risk alleles, further elucidation of disease mechanisms through Mendelian traits might be the strategy to adopt [2].

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Pathophysiology of Gastro-oesophageal Reflux Disease

72

Silvia Salvatore and Geoffrey Davidson

Introduction

Gastro-oesophageal reflux is an extremely common paediatric problem, and its pathogenesis is complex and multifactorial involving anatomic, hormonal, environmental, and genetic factors (Fig. 72.1). The difference between physiological reflux (GER) and gastro-oesophageal reflux disease (GERD) is often blurred by the anxiety engendered in parents, particularly first-time parents, by symptoms such as vomiting and irritability in young infants.

Epidemiological data show that spilling or regurgitation in infancy is very common and decreases spontaneously and almost completely by 1 year of age [1, 2]. It is generally accepted that infants with regurgitation are thought to have an excellent long-term prognosis. It is classically stated that infant regurgitation is physiological and rarely requires medical intervention needing only explanation and reassurance.

However, somewhere between 5 % and 9 % of infants have ongoing and troublesome GERD [3, 4]. If these GERD symptoms continue after the age of 3 or older [5], they are more likely to persist into adulthood.

Reflux oesophagitis is reported to occur in 2–62 % of children with symptoms of GERD and Barrett's oesophagus (BE) in 0.1–3 %, and refractory GERD requiring surgery is seen in 6–13 % [6]. More than 50 years ago, in the absence of reflux treatment, oesophageal strictures were reported in about 5 % of children with reflux symptoms [7]. Nowadays, oesophageal stenosis and ulceration in children have become extremely rare.

Children with neurological impairment, cystic fibrosis, and repaired oesophageal atresia are known to be children at risk for severe reflux and subsequent complications.

Research into the physiology and pathophysiology of GER has advanced markedly over the last decade with the development and use of new technologies such as micro-manometry, noninvasive breath testing, and multichannel intraluminal impedance (MII) [8]. These techniques have demonstrated that reflux episodes occur most often during transient lower oesophageal sphincter relaxations (TLESRs) unaccompanied by swallowing,

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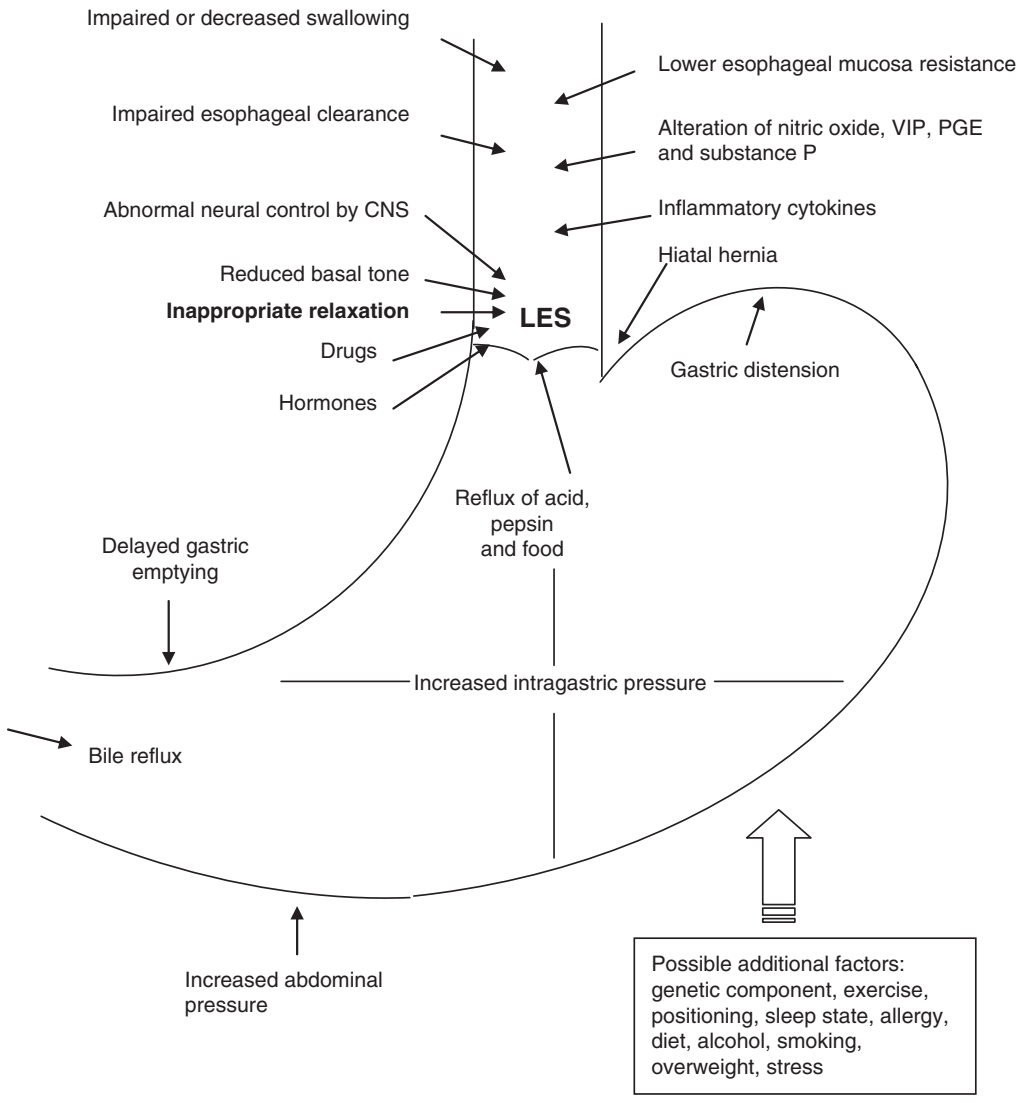

(modified from: Salvatore S, Hauser B, Vandenplas Y. The natural course of gastro-oesophageal reflux. Acta Paediatr 2004;93:1063-1069)

Fig. 72.1 Factors involved in the pathogenesis of GERD. *CNS* central nervous system, *LES* lower oesophageal sphincter, *PGE* prostaglandin E, *VIP* vasoactive intestinal peptide. Inappropriate relaxation is typed in blood as it represents the most important pathophysiological mechanism in GER

which permit gastric contents to flow into the oesophagus [9, 10]. However, in patients with severe reflux oesophagitis, many GER episodes occur unrelated to TLESRs [11]. A minor proportion of reflux episodes occur when the LES pressure fails to increase during a sudden increase in intra-abdominal pressure or when LES's resting pressure is chronically reduced [10].

In the past decade, GER and/or GERD has become a major part of paediatric gastroenterological practice. This chapter will discuss more recent advances in our knowledge with regard to the pathophysiology of GERD.

Definitions

Gastro-oesophageal Reflux and Gastro-oesophageal Reflux Disease

GER is the passage of gastric contents into the oesophagus [12] and is a normal physiologic process occurring several times per day in healthy infants, children, and adults. Most reflux episodes are asymptomatic, brief, and limited to the distal oesophagus.

'Physiological GER' is defined as GER without associated symptoms, during the first months of life, with regurgitation being the most visible symptom occasionally accompanied by vomiting. This usually resolves spontaneously within the first year of life [2].

In contrast, GERD is present when the reflux of gastric contents causes troublesome symptoms and/or complications [13].

Primary and Secondary GERD

Primary GERD results from a primary motility disorder and dysfunction of the LES. Primary peristalsis is the most common motor event after reflux and accounts for up to 90 % of initial and subsequent motor activity [14].

Secondary GERD is caused by diseases within or outside the gastrointestinal tract (i.e. cow's milk allergy, idiopathic pyloric hypertrophy, metabolic or respiratory disorders, infections, and intracranial hypertension).

The symptoms of primary and secondary reflux are similar, but a distinction is conceptually helpful in determining the therapeutic approach. Secondary GER is not further discussed in this chapter.

Mucosal Resistance

The oesophageal mucosa contains established protective mechanisms operating within the pre-epithelial, epithelial, and post-epithelial compartments.

The stratified squamous epithelium protects against rough food material that is swallowed, but its integrity is compromised by recurrent, chronic exposure to refluxate of strong acid or alkali [10]. Oesophageal glands are irregularly distributed, are small, contain only mucous cells, and lubricate the swallowed bolus during its passage. Bicarbonate secretion capacity of the human oesophagus is small and of little clinical relevance for mucosal defence [15].

Oesophageal mucosal dilated intercellular spaces (DISs) are frequently observed in patients with non-erosive reflux disease (NERD) and patients with oesophagitis. The specificity of DIS is questionable, as it is present in up to 30 % of asymptomatic healthy subjects and in patients with other oesophageal disorders. DIS occurs in parallel with a drop in potential difference, diminished transepithelial resistance, and increased oesophageal mucosal permeability. These alterations arise with exposure to acid and pepsin during GER, but the exact pathway of damage to the intercellular junctions remains unclear and seems to be multifactorial. Other noxious contents of the refluxate, such as bile acids, are harmful, and DIS can also be induced by acute psychological stress. DIS can disappear after treatment with proton-pump inhibitors (PPIs); however, this is not the case in all NERD patients [16]. Oesophageal mucosal DIS may be important for symptom perception in NERD. Patients with NERD might have DIS even in the proximal oesophagus [17]. In 14 healthy adults, oesophageal perfusion with acid or weakly acid solutions, with or without bile acids, provoked DIS in the 'exposed' and in the more proximal 'nonexposed' oesophageal mucosa. However, in spite of the presence of perfusion-induced DIS, most healthy subjects do not perceive heartburn [17].

Since refluxed acid and pepsin always act from the luminal side of the mucosa, protective factors, like the epidermal growth factor operating as a part of the pre-epithelial defence, are essential in the maintenance of the integrity of the oesophageal mucosa. The resistance of the mucosa to the noxious effect of the refluxed material (acid, pepsin, chymotrypsin and trypsin, bile, etc.) is different from person to person and seems genetically determined. Prostaglandin E2 and nitric oxide (NO) are said to be protective (in

low concentrations) and detrimental (in high concentrations) for oesophageal mucosal integrity. The release of prostaglandin differs for the subtypes and in the function of the composition of the refluxed material [17].

Nitric oxide is the inhibitory neurotransmitter in the oesophageal muscle, is responsible for the latency gradient of oesophageal peristalsis, and is involved in LES relaxation [18]. However, the mechanism of peristalsis in the oesophagus is complex and involves both central and peripheral mechanisms.

Composition of Refluxate

In adults, the severity of oesophageal injury has long been attributed to oesophageal acid exposure [19], and healing of reflux oesophagitis has been directly correlated with the maintenance of the intragastric pH above 4.0 [20]. However, more recent reports failed to show a correlation between the results of a classic pH-metry and oesophageal histology [20]. The relation between reflux symptoms, endoscopic or histologic findings and exposure of the oesophagus to acid is complex [21]. In paediatric patients, the concordance between the results of pH-metry and oesophageal histology has been debated, denied or sustained [22].

The advent of MII-pH has demonstrated that nonacid (now defined as weakly acidic when oesophageal pH is between 4 and 7) reflux is as common as acid reflux (pH<4) and significantly more frequent than acid reflux in the first months of life and postprandial time because of gastric buffering related to frequent meals or milk.

Nonacid, mixed gastric, and duodenal reflux and impaired oesophageal clearance have been suggested to play a role in determining oesophageal mucosal injury. In a small paediatric study group, MII-pH results failed to identify parameters correlating with the presence of histologic oesophagitis. The duration and number of acid, weakly acid and alkaline, and gas reflux episodes were comparable in children with and without oesophagitis [22].

Reflux of pepsin and trypsin may exert an aggressive effect on the oesophageal epithelial cells and mucosa due to their proteolytic actions (maximum at pH 2–3 for pepsin, but with action up to pH 5.5, and at pH 5–8 for trypsin) [10]. The exact role of bile reflux or duodeno-gastric reflux is as yet poorly understood. Conjugated or deconjugated bile salts exert a predominant noxious effect which is pH dependent [23].

The myogenic tone of the LES is modulated by a variety of neurohormonal influences.

The following increase LES pressure: muscarinic M2 and M3 receptor agonists, α-adrenergic agonists, gastrin, motilin, substance P, prostaglandin F2α, gastric contractions, alkalinisation and proteins in the lumen [18].

The following decrease LES pressure: oesophageal balloon dilatation, the presence of fat in the duodenum, progesterone, prostaglandin E, β-adrenergic agonists, atropine, cholecystokinin, glucagons, vasoactive intestinal peptide (VIP), nitric oxide (NO) dopamine, secretin, oestrogen, nicotine, alcohol, mint, caffeine and chocolate [18]. VIP, NO, and cholecystokinin induce TLESRs, and L-arginine, the endogenous source of NO, prolongs TLESRs although NO levels were equal in biopsies of normal and inflamed oesophageal mucosa [18].

Upper and Lower Oesophageal Sphincter (LES)

The upper oesophageal sphincter (UES) and LES are not anatomically distinct muscles, but differ from that of the oesophageal body by their thickened muscle layer and high-pressure zone. Studies in children have demonstrated UES pressures comparable with those in adults (40–50 mmHg) and UES relaxation in response to swallowing. The pressure of the UES differs in relation to the kind of material present in the oesophagus: it disappears when there is air as in belching, whereas it increases when there is ingested material or acid refluxes [10]. In addition, basal UES pressure is highly dependent on the state of arousal and behaviour, varying from 18 mmHg during rest to 56 mmHg when crying

[24]. These findings are also similar to that noted in preterm infants >33 weeks postmenstrual age where the motor mechanisms regulating the UES are well developed [25]. UES pressure also increase with discomfort and straining [24, 26].

The LES consists of a segment of specialised muscle that is contiguous with and just exterior to the smooth muscle of the oesophagus and the stomach and is a functional barrier representing a zone with an intraluminal pressure greater than that of the stomach and oesophagus. In adults, this high-pressure zone has a length of 3–6 cm and a pressure of about 20 mmHg (range, 10–40 mmHg). An absolute pressure of less than 6 mmHg is required for GER [27].

In infants the length of the LES is only a few millimetres, but despite this, studies have shown that mean resting LES pressure at the onset of relaxation in preterm infants is not dissimilar to that in adults with a mean LES pressure around 20 mmHg [28, 29].

The LES relaxes 2.5 s after the initiation of a swallow, well before the arrival of the bolus, and remains open for 10–12 s, until the bolus has passed [10]. There is also a postprandial decrease in LES pressure in both normal and GERD patients. The LES is characterised by tonic muscle innervated by inhibitory and excitatory neurons. The LES maintains tonic closure due to its myogenic property [28]. Relaxation of the LES without oesophageal peristalsis may occur during belching, vomiting and TLESRs. Increased abdominal pressure is, in the main, associated with increased sphincter pressure, but gastric distension is accompanied by a fall in LES pressure or by TLESRs that can last for 10 up to 17 s [30]. It is believed that these responses are mediated via vagal reflexes and are inhibited by GABA-β agonists such as baclofen. The larger the meal, the more TLESRs, and equally, the greater the gastric secretory volume and the higher the intragastric osmolarity, the more TLESRs [9, 10]. Stimulation of mechanoreceptors in the gastric fundus, or stretching of the gastric fundus, initiates vago-sympathetic-mediated reflexes resulting in these TLESRs. TLESRs are also more frequent in the seated position than in supine position.

Using a micro-manometric assembly incorporating a micro-pH electrode recorded oesophageal motility and pH in 36 preterm and term infants showing that TLESRs were the predominant mechanism of GER, triggering 50–100 % of GER episodes (median, 91.5 %) [31]. Gastric distension (by feeding) also stimulated TLESRs. Abdomino-thoracic straining significantly increased the occurrence of GER in association with TLESRs. In infants with GERD, the number of TLESRs overall was similar to normals, but the proportion of TLESRs accompanied by acid GER was significantly higher than in normals (16.5 % vs. 5.7 %, respectively; $p < 0.001$) [32].

Oesophageal Clearance

Oesophageal clearance is influenced by at least three factors: oesophageal peristaltic waves, gravity, and saliva. Oesophageal clearance mechanisms are well developed by at least 31 weeks of postmenstrual age [32]. It is also important to note that the more proximal the reflux reaches, the more likely a swallow will occur leading to not only bolus clearance but also assistance in airway protection [33].

Oesophageal clearance of acid reflux consists of an initial volume clearance followed by neutralisation of the acidified mucosa by swallowed saliva (chemical clearance). The pH of saliva varies from neutral to alkaline and contributes to the neutralisation of the refluxed acid. Moreover, the bolus effect of swallowed saliva will increase primary oesophageal peristalsis and help oesophageal clearance from the refluxed material [10]. Saliva flow increases concurrently with the onset of heartburn, a phenomenon called ‘water brash’. Oesophago-salivary reflexes become mainly effective in prolonged episodes of GER [8]. Impaired oesophageal clearance of acid and decreased salivary function have been reported in patients with reflux oesophagitis, especially in those with neurological compromise [10]. The important reduction of saliva secretion and swallowing rate during quiet sleep may contribute to delayed oesophageal clearance of nocturnal reflux episodes.

Secondary peristalsis is caused by GER and starts at the highest level; the refluxed material reaches in the oesophagus. It contributes to oesophageal clearance of remnants of the refluxed material that were not cleared by a primary peristaltic wave. The larger the volume of refluxed material, the higher the amplitude of the secondary waves. Secondary peristalsis can be produced experimentally by inflation and deflation of an oesophageal balloon [10]. Hot substances increase speed and amplitude of peristaltic contractions; cold swallows have the opposite effect. Pain, at least in adults, delays oesophageal clearance [10].

Impedance-pH data has demonstrated that acid (chemical) clearance is significantly longer than bolus clearance at all ages. Combined MII-pH and oesophageal manometry (MII-EM) has recently demonstrated that patients with erosive oesophagitis exhibit a significantly lower percentage of complete bolus transit and a longer mean bolus clearance time (MBCT) compared to healthy controls and non-erosive reflux disease (NERD) patients [34].

Proximal Extent of GER

The clinical relevance of the proximal extension of a reflux episode in generating symptoms needs further research. In infants and children, a stronger association between symptoms and proximal reflux than with non-proximal reflux was sustained by some authors [35, 36], but not confirmed by others [37]. Proximal extension of reflux is frequent but is not necessarily a cause of symptoms. As expected, the proportion of proximal reflux is higher for 'vomiting' as a symptom than for all the other symptoms.

Effect of Body Position on GER and Gastric Emptying

The recent combination of manometry with impedance has provided the ability to explore the effect of body position and its relationship to GER to the rate of gastric emptying (GE) [33].

In an initial study of ten healthy preterm infants, TLESRs were the predominant mechanism of reflux, triggering 83 % of GER. Of the 92 TLESRs recorded, 17 % were not associated with reflux. Infants studied in the right lateral position had significantly more GER ($p<0.01$), a higher proportion of liquid GER ($p<0.05$), and faster GE ($p<0.005$) when compared with infants studied in the left lateral position [38].

A 'crossover position study' was carried out in another cohort of ten healthy preterm infants, and postprandial evaluation confirmed more liquid GER in the right than in the left lateral position (median, 9.5 [range, 6.0–22.0] vs. 2.0 [range, 0.0–5.0] episodes/h; $p=0.002$). Gastric emptying was faster in the right than in the left lateral position (37.0 ± 21.1 vs. 61.2 ± 24.8 min; $p=0.006$) [38].

Similar findings were reported by Corvaglia et al. in 22 preterm infants with regurgitation and postprandial desaturations. The number of acid- and nonacid reflux episodes was significantly smaller when the subjects were in the prone and left-side position in comparison to those in the supine and right-side positions [39]. The left-side position showed the lowest oesophageal acid exposure (0.8 %) in the early postprandial period, whereas the prone position showed the highest oesophageal acid exposure (acid exposure, 5.1 %) in the late postprandial period [44].

A further study using combined MII-pH with epigastric impedance for 3 h was carried out in 30 newborns referred for apparent life-threatening events and signs of GERD [40]. An inverse correlation was evident for reflux frequency and gastric emptying velocity ($R^2=0.94$; $p<0.001$) and between acid refluxes and the gastric filling state ($R^2=0.95$; $p<0.001$), whereas a positive correlation was found between the reflux level and the gastric filling state ($R^2=0.52$; $p<0.05$) [45].

Eight healthy preterm infants studied using an oesophageal impedance-manometry catheter incorporating an intragastric infusion port showed that more TLESRs were triggered in the right lateral position compared with left lateral position (4.0 [3.0–6.0] vs. 2.5 [1.0–3.0]; $p=0.027$). First TLESRs occurred at a significantly lower infused volume and percentage of feed in the right compared with left lateral

position (10.6±9.4 vs. 21.0±4.9 mL; $p=0.006$) (17.6±15.5% vs. 35.4±8.02%; $p=0.005$). TLESRs and GER were triggered at volumes unlikely to induce gastric distension [41].

Delayed GE has been reported in 10–15% of adult and in 28–50% of paediatric GERD [42, 43]. Delayed GE can be secondary to a number of conditions including infections (*Rotavirus*, *Helicobacter pylori*), food allergy, prematurity, drugs (opioids, anticholinergics), previous surgery, eosinophilic gastroenteropathy, metabolic (hypokalemia, acidosis), endocrine (diabetes mellitus, hypothyroidism), muscular (visceral myopathy, myotonic dystrophy) and neuronal (cerebral palsy, vagotomy, pseudo-obstruction) disorders [43].

Diagnosis relies on clinical observation, confirmed by gastric emptying scan, antroduodenal manometry, ultrasound (after a test meal), electrogastrography, 13C-octanoic acid breath test, and impedance epigastrography. As overlap between healthy and affected subjects exists, the interpretation of these tests is often challenging.

Gastric emptying studies in 36 infants using the 13C-octanoic acid breath test showed similar results in GERD patients and normals [31]. For all infants, mean half GE time was 33 min, and breastfed infants had faster rates. Infants receiving feeds at two, three, or four hourly intervals had different GE times, with longer intervals between feeds being associated with significantly slower GE most likely due to differences in feed volumes administered (smaller in the more frequently fed infants). Delayed GE in infants and children does not seem to correlate with symptoms due to GERD or in fact be a contributor to it [38].

Effect of Frequency and Duration of GER

The frequency and duration of reflux episodes may determine the response of oesophageal nociceptors. Repeated noxious stimuli or one very strong stimulus can sensitise both afferent types of fibres (C-unmyelinated and A-delta) to respond to typical non-noxious stimuli as very painful. Thus, a small oesophageal distension as occurs in belching, minimal regurgitation, or even the passage of a swallowed food bolus may be experienced as very painful. The sensation of pain is transported to the brain via calcitonin gene-related peptide (CGRP) and substance P which determines smooth muscle contractions, vasodilatation and increased mucosal permeability. Substance P is also released when there is tissue damage, as in oesophagitis, inducing a vicious cycle: the more tissue damage, the more substance P and the greater the noxious effect of the refluxed material [10]. Substance P also causes histamine release from the mast cells in the alveoli and thus contributes to bronchospasm and GER-related respiratory symptoms.

Hiatus Hernia and GERD

Hiatus hernia refers to herniation of gastric cardia in the most common type I or sliding hiatal hernia through the oesophageal hiatus of the diaphragm. The prevalence of hiatal hernia in infants and children is unknown. Most adults with hiatal hernias are asymptomatic. However, there is a high prevalence of hiatal hernia in adults with reflux symptoms and oesophagitis. The likelihood of developing reflux disease is directly related to the size of the herniation. Hiatal hernia is more frequent within an affected family, and severe hiatal hernia may be an autosomal dominant inherited disorder [44]. Hiatal hernia is more frequent in different conditions that all have severe GER in common, such as neurological impairment, chronic lung disease (especially cystic fibrosis), oesophageal atresia, etc., and in Barrett's oesophagus [45]. In patients with a hiatal hernia, the LES is dislocated into the thorax, and the (local) negative pressure (exacerbated during inspiration) facilitates gastric reflux (due to the abdominal positive pressure).

Genetic Influence

The genetic influence on GER is supported by increased GER symptoms in relatives of GER disease patients [46] and by higher concordance

for GER in monozygotic than dizygotic twins [47]. Moreover, a locus on chromosome 13q, between microsatellite D13S171 and D13S263, has been linked with severe GER disease in five multiple affected families [48], but not confirmed in another five families, possibly due to genetic heterogeneity of GERD and different clinical presentations of patients recruited [49]. Familial inheritance of hiatal hernia does also occur with a likely autosomal dominant mode of inheritance [44]. More recently a GERD susceptibility gene (collagen type III alpha 1) has been discovered and shown to be a male risk factor for hiatus hernia [50]. It is not known how important genetic factors are in explaining the differences in presentation and the natural course of GER.

Extraoesophageal Manifestations of GERD

Respiratory

Nearly every single respiratory manifestation (subglottic stenosis, stridor, recurrent croup, laryngomalacia, apnea, asthma, bronchitis, pneumonia, chronic sinusitis and recurrent otitis media) has been reported in relation to GERD [12, 51]. GERD is reported in 40–75 % of children with chronic respiratory symptoms, especially when the symptoms are nocturnal and unresponsive to classic treatment [12].

A history-based diagnosis of GER was made by Chouhou, a French physician, in 18 % of a population of unselected infants younger than 10 months of age. Interestingly, he reported a higher incidence of infants with more than three episodes of rhinopharyngitis (18 % versus 16 %), more than three episodes of otitis media (11 % versus 5 %), and more than two episodes of bronchitis (3.6 % versus 2.8 %), during the first year of life [52].

In a large paediatric case-control study, GERD has been associated with an increased risk for sinusitis, laryngitis, asthma, pneumonia and bronchiectasis [53]. A systematic review on the association between GERD and asthma in children found 20 articles that described 5,706 patients, where the prevalence of GERD in asthma was highly variable (19.3–80.0 %) with a pooled average of 22.8 % with GERD symptoms, 62.9 % of 789 patients with abnormal oesophageal pH and 34.8 % of 89 patients with oesophagitis. Only five studies included controls and enrolled 1,314 patients with asthma and 2,434 controls without asthma. The average prevalence of GERD was 22.0 % in asthma cases and 4.8 % in controls (pooled odds ratio: 5.6 [95 % confidence interval: 4.3–6.9]) [54].

GER may be causing respiratory symptoms through a direct relation by (micro-)aspiration or by neurogenic reflex. The reverse may also be happening: respiratory difficulties cause greater respiratory breathing efforts and thus more pronounced negative intrathoracic pressures, provoking GER [9]

The relationship between respiratory manifestation and GERD remains controversial mostly because of the difficulty demonstrating the association between symptoms and reflux and the improvement with reflux treatment.

Apnea and Bradycardia

Frequent apnea and bradycardia, particularly with feeding, are widely accepted to be a common clinical correlate of reflux disease [10]. It is hypothesised that GER may be a direct or indirect trigger for apneic episodes via the mechanisms related to poor coordination of swallowing with breathing and neural reflex mechanisms initiated by chemical stimulation of the larynx/pharynx or oesophageal distension. Alternatively the likelihood of GER occurring may be exacerbated by a transient increase in the gastro-oesophageal pressure gradient resulting from airway obstruction [9]. The evaluation of the temporal association between reflux and apnea requires prolonged simultaneous monitoring of both reflux and respiratory events [9]. Conflicting findings of either little or no association or an association between apnea and GER, recorded by either pH probe of MII, have been reported [55, 56].

Otitis Media

Tasker et al. [57] were the first to describe the presence of gastric juice in the middle ear of children with otitis media by finding pepsin in middle ear effusions. Eighty three percent of 54 effusions contained pepsin/pepsinogen at concentrations of up to 1,000-fold greater than those in serum. A later study from He et al. [58] evaluated a larger cohort of 152 children and showed only 14 % had pepsin in middle ear fluid, and that the incidence was significantly higher in the older age groups.

This concludes the summary of the pathophysiology of GER and GERD in children.

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73 The Oesophageal Mucosa: To Barrett's and Beyond – The Genesis of Oesophageal Injury and Cellular Mutations

N. Haider, A. Day, and Spencer W. Beasley

Introduction

Gastro-oesophageal reflux (GER) is a normal physiological phenomenon in infants and young children, occurring as a consequence of immaturity, a transient relaxation of the lower oesophageal sphincter and the relative short length of intra-abdominal oesophagus. Gastro-oesophageal reflux disease (GERD) can be defined as reflux leading to symptoms and/or complications and may be seen in infants or older children. Reflux of gastric contents in GERD is frequent during the day but is more common after feeds and when recumbent. Normal mechanisms tend to clear the refluxate in the oesophagus quickly, thus avoiding any mucosal damage or injury. In some conditions such as oesophageal atresia, there may be delayed oesophageal clearance, prolonging the time the refluxate is in contact with the oesophageal mucosa.

Chronic or frequent reflux may result in changes to the lower oesophagus including local inflammation, erosions or ulcerations. During the healing process, the damaged areas are usually re-reepithelialized by normal squamous epithelium. This healed area may, however, undergo a metaplastic change and be replaced by columnar epithelium, which can be gastric, fundic or of intestinal type [1]. The development of intestinal type columnar epithelium with goblet cells is termed Barrett's oesophagus (BE). The American society for gastrointestinal endoscopy (ASGE) defines Barrett's oesophagus as "specialized intestinal metaplasia of the distal esophagus irrespective of the length of segment involved" [2]. BE can lead to dysplastic changes and a subset of individuals subsequently develop adenocarcinoma. Overall, columnar lining of the oesophagus confers a 30–40-fold increase in the incidence of carcinoma. Although the precise pathogenesis of BE is not completely understood, recent data illustrates the importance of chronic acid or bile reflux with cycles of injury, inflammation and repair leading to genotoxicity.

Endoscopic Appearance of Barrett's Oesophagus

BE is able to be seen endoscopically less than 50% of the time and, otherwise, is determined only during histological examination of mucosal biopsies. When it is evident macroscopically, the typical appearance is of a circumferential irregular, "salmon pink" area with irregular edges at or above the gastro-oesophageal junction (Fig. 73.1).

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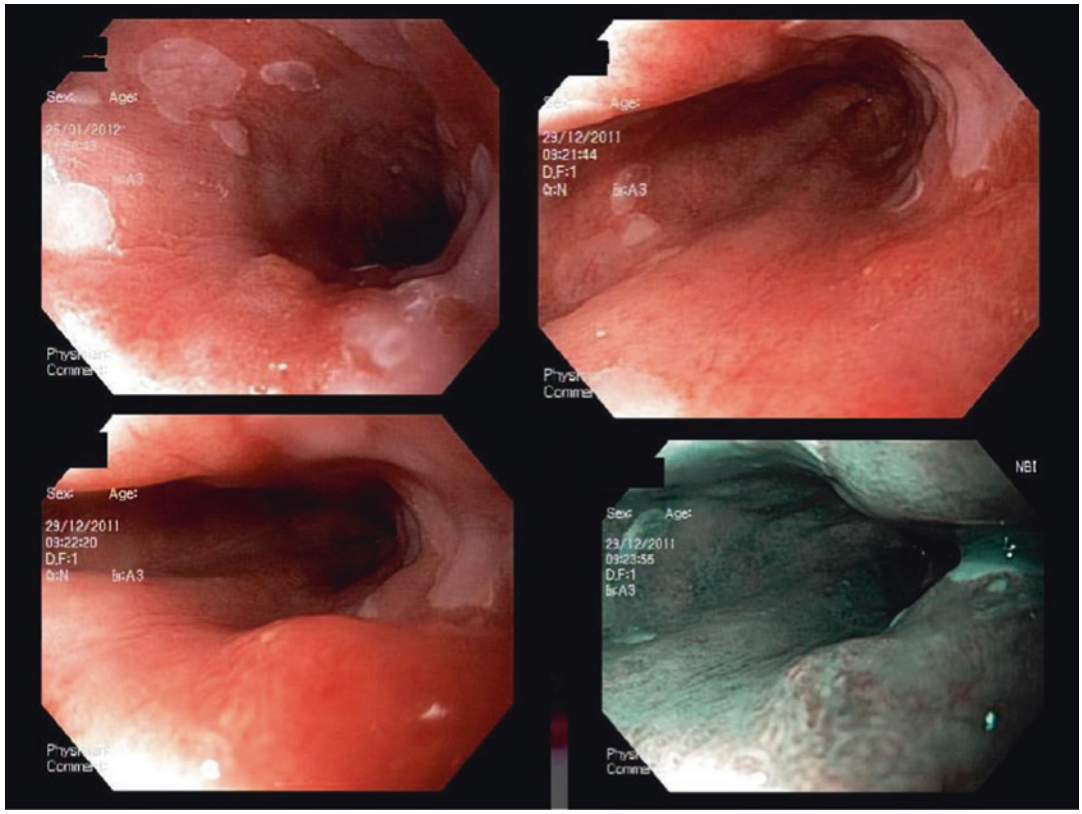


Fig. 73.1 Long-segment Barrett's oesophagus, nodule at 5 o'clock under white light and narrow-band imaging (*bottom right picture*)

Other features are of irregular or raised areas, plaques or ulcerations. Areas of metaplastic BE may be present in conjunction with dysplastic changes (low grade or high grade) or even carcinoma. Plaques, areas of increased vascularity, depressions or ulcerations in the mucosa and slight villiform elevations of the mucosa can represent dysplasia, but none of these are pathognomonic. About 50% of cancers detected at screening endoscopies are early-stage cancers (Table 73.1).

Table 73.1 Features of dysplasia and malignancy on endoscopy [3]

No	Endoscopic feature	Significance
1	Columnar epithelium	30–40× increased incidence of carcinoma
2	Plaques	May indicate dysplasia
3	Areas of increased vascularity	May indicate dysplasia
4	Depressed or elevated areas	May indicate dysplasia
5	Villiform elevations	May indicate dysplasia
6	Circumscribed, polypoid or protruded lesions	May represent malignancy

Endoscopic Appearance of Early Malignancy

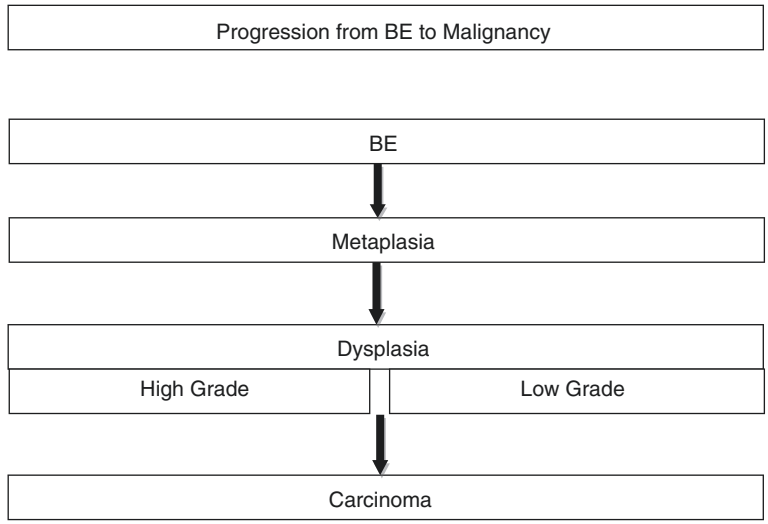
Early superficial malignancy is cancer confined to the mucosa and submucosa without lymph node metastasis. The endoscopic appearance can be divided into three types as described in Table 73.2.

As would be expected, type 2 is the most difficult to diagnose by virtue of its very subtle features, and confirmation relies on histological examination.

Table 73.2 Macroscopic appearance consistent with early superficial malignancy [3]

Type	Macroscopic appearance
Type 1	High (elevated more than 3 mm)
	Low (elevated less than 3 mm)
Type 2	Superficial flat type
Type 3	Depressed or excavated

Progression from Normal Mucosa to Malignancy



As a result of GER and chronic inflammation, the lower oesophageal mucosa may undergo carcinomatous change. The presumed sequence of events is the development of low-grade dysplasia (LGD), which progresses to high-grade dysplasia (HGD) that ultimately culminates in oesophageal adenocarcinoma. This progression from normal→metaplasia→cancer is characterized by overexpression of growth factors and inducible nitric oxide synthase and cyclooxygenase-2 [4]. There is recruitment of cells from G0 to G1, loss of control at G1/S phase transition and accumulation of cells in G2 [5]. Cyclin D1 is also overexpressed in Barrett's metaplasia, dysplasia and cancer [6]. Patients with BE with overexpression of cyclin D1 are more likely to develop adenocarcinoma compared to those without [7, 8]. Overexpression of telomerase has also been shown in BE as well as in other dysplastic and malignant lesions. This suggests that telomerase is upregulated in early neoplastic progression of BE. Various studies have reported genetic and epigenetic abnormalities in oesophageal carcinoma. Different genes may be important at different stages of tumour progression. Epigenetic changes, however, are thought to precede genetic changes. Nonsteroidal anti-inflammatory drugs (NSAIDs) appear to have a cytoprotective effect for the development of oesophageal adenocarcinoma. Long-term use of acid suppression can decrease cellular proliferation and can potentially stabilize the fragile sites [9, 10].

Risks of Malignancy and Prediction in Barrett's Oesophagus

BE has a 10% potential of turning into a malignant adenocarcinoma. Five-year survival of oesophageal adenocarcinoma is only about 10% unless detected at an early stage [11]. Mutations of p53 are common in oesophageal cancers [12]. These mutations increase with progression along the metaplasia→dysplasia→carcinoma sequence. The loss of heterozygosity (LOH) at p53 locus has been identified in 94% of cancer related to BE, and p53 mutations are seen in 88% cases of oesophageal adenocarcinoma [13]. LOH at 5q (APC locus) has also been found in p53 in 75% of Barrett's cancers. P53 mutation and allelic loss are an early event and can be identified in the stage of high-grade dysplasia before aneuploidy develops [14]. Zhuang et al. [15, 16] found LOH at APC locus in 50% of oesophageal adenocarcinomas with identical patterns of allelic loss in adjacent HGD in all cases. They also explained allelic loss in 40% of adjacent non-dysplastic areas in BE confirming that APC loss is an early event. While LOH at APC locus is

common in oesophageal adenocarcinoma, APC mutations are quite rare. Tumour-suppressor genes including CDKN2A/p16, VHL, Rb and DCC have also been shown to undergo LOH in over 50% cases of adenocarcinoma. Barrett et al. [17] showed LOH at CDKN2A/p16 locus in 75% cases. LOH was seen in both cancer and dysplasia and preceded aneuploidy. This suggested that LOH is an early event in cancer progression.

Putative Pathogenic Mechanism of Damage in Barrett's Oesophagus

BE is an acquired premalignant condition secondary to the effects of chronic reflux [18, 19]. Persistent exposure to acid and bile salts results in genetic alterations which progress with time from dysplasia to oesophageal adenocarcinoma [20]. Exposure to acid and bile salts changes oesophageal mucosa and can promote regeneration with columnar rather than squamous epithelium [21]. While a number of risk factors have been linked to the development of oesophageal carcinoma in adults, the most significant factor appears to be GERD. Obesity, hiatus hernia, diet high in fat and cholesterol and low in antioxidants and fibre and smoking are all thought to contribute to the development of oesophageal cancer but have a less pronounced effect [22–25]. It is unclear, at the molecular level, exactly how GERD leads to carcinoma.

Possible mechanisms include:

1. Prolonged acid and bile reflux causes mucosal injury either directly or via an inflammatory process [26–32].
2. The reduced antioxidant capacity of Barrett's oesophagus plays a role in tissue injury and genetic damage [33, 34].
3. Oxygen free-radical damage may be contributory as shown in animal models [35].

Secondary Healing and Damage by Acid and Bile Salts

Acid and bile salt exposure results in a range of biological effects to the oesophageal epithelium. Jolly et al. [29] have demonstrated specific damage patterns including DNA strand breaks in oesophageal cell lines, FLO 1 and HET 1, when exposed to acid and bile salt in vitro. The acid-induced damage to epithelial cells appears to be time dependent. In addition, acid exposure of epithelial cells stimulates activation of MAP kinase and cyclooxygenase-2 expression, as well as modifying proliferation and differentiation rates [31, 36–40]. DNA damage results directly from the acid component of the refluxate. Acid suppression results in further damage by bile salts which are rendered inactive at a lower pH.

FLO 1 cells derived from oesophageal adenocarcinoma have been shown to withstand longer acid exposure. These cells can withstand more noxious stimuli in part because they are derived from adenocarcinoma and possess more cytoprotective properties. In contrast, HET 1 cells derived from normal squamous epithelium show an enhanced sensitivity to damage in an acid milieu [29]. Consistent with this, patients with BE have a higher incidence of bile reflux compared to those with oesophagitis alone or control groups [41–43].

Cellular damage from bile acids includes stimulation of cell proliferation and tumour invasiveness, inhibition of apoptosis and modification of the promoter genes involved in DNA synthesis, DNA repair and oxidative stress. Some of these effects may be mediated through a bile acid-specific nuclear receptor, FXR via protein kinase C activation [44]. In addition, ex vivo exposure of BE tissue to bile salts has been shown to upgrade cyclooxygenase-2 expression and modify cell proliferation rates [31, 39]. Genetic alterations can lead to increased malignant potential [45]. It is possible that alkaline GERD causes DNA damage which results in changes at the molecular level. The promoting effects of bile salts are:

1. Increased rates of proliferation
2. Reduced differentiation
3. Elevated cyclooxygenase-2 expression [36, 38, 39]

Other possible mechanisms include topoisomerase II-mediated DNA damage as shown by Xiao et al. [20] in a mouse model or damage through reactive O2 species (ROS).

Injury and Mutations at a Cellular Level

DNA damage affects fragile sites of a chromosome. These are areas of rearrangement or loss that are observed in many malignancies. Lisa et al. [11] have reported copy number loss/loss of heterozygosity (LOH) at 56 fragile sites in patients with early BE. They found LOH in high frequency at several sites: FRA3B (81 %), FRA9A/C (71.4 %), FRA5E (52.4 %) and FRA4D (52.4 %). They also found LOH in lower frequency at other loci: FRA1K (42.9 %), FRAXC (42.9 %), FRA12B (33.3 %) and FRA16D (33.3 %). These data suggest that deletion and genomic instability at certain fragile sites could act as a biomarker for genetic damage in (BE) and also be a potential biomarker of cancer risk. Unlike in many other cancers, the LOH and copy loss observed in BE are narrow and well conserved in a subset of fragile sites, most commonly FRA3B. While wide-ranging deletions at FRA3B over a broad range, 300 KB to over 2 MB, have been reported in other cancers, deletions in the subregion (60.2–60.6 MB corresponding to FHIT exons 4–5) have only been reported by Lisa et al. The high frequency and uniformity of alterations in BE may reflect a common aetiology of genotoxic stress. In BE, this is thought to be oxidative damage as a result of direct effect and via the effects of O2 free radicals. Fragile site damage is induced by replication stress in vitro [46, 47], meaning that fragile sites may be the first regions of a genome to have mutations in vivo when exposed to a carcinogen.

Are the Mucosal Changes Reversible?

Can an antireflux procedure (ARP) result in regression of BE and reverse the dysplasia? Regression after an ARP is not proven, and there are only occasional reports of reversal of BE epithelial changes following surgical correction of reflux [48–52]. Most studies, have failed to demonstrate reversible changes following an ARP [53–57] perhaps indicating that there might be an ongoing risk of dysplasia and malignancy. Williamson et al. [58–61] reported three cases of malignancy after an ARP, while Stein and colleagues identified two further cases. Mc Donald et al. [62] demonstrated that after a failed antireflux procedure, the progression to cancer occurred during the first 3 years. The fact that all three of their cases occurred in the early follow-up period raises the possibility that changes were already present before surgery but were not detected. If so, it could be argued that there was no progression in this group of 113 patients. There is no strong evidence to suggest that ARP will reverse the changes or BE will necessarily progress to malignancy. The Mc Donald study [62] did not show any cancers in the late follow-up period, and McCallum's study [59] showed a definitive decrease in the incidence of dysplasia following an ARP. These observations would suggest that ARPs might play some role in preventing the development of new cancers.

How long does it take for these changes to develop? Low- or high-grade dysplasia which occurs in almost 20 % of patients with BE is currently the most reliable marker for progression to oesophageal carcinoma [63–66], but the process is clearly and not always predictable [64, 67]. Some have suggested that HGD can be present for several years without progression to carcinoma and may even be reversible [66, 68–70]. Altorki et al. [71] demonstrated that carcinoma was already present in 30 % cases of patients undergoing surgery for HGD.

How Long Does It Take to Progress from Barrett's Oesophagus to Malignancy?

An elegant study by Thiesen et al. [72] gives us some insight into the time frames relating to progression from the time of diagnosis of BE to when a carcinoma develops. They showed that progression from metaplasia to LGD develops in a median of 24 months, HGD 33 months and cancer 36 months, but it is not clear how long these patients had BE prior to their initial assessment. Schnell et al. [70] found a mean surveillance period of 7.3 years before cancer was detected. However, their study group included patients

with advanced cancer as well as early cancer. Early cancer was detected in their cohort of patients at about 4 years. Hameeteman et al. in a prospective study showed that it took between 1.5 and 4 years for patients to progress from LGD to cancer. This also showed HGD may be present for as long as 3.5 years before progression to cancer occurs [64]. One patient in Thiesen's study who developed cancer after a Nissen fundoplication had a time lag of 2 years before cancer was diagnosed. Though most patients with BE never develop cancer, there is a small subset that does. Despite considerable research we are still uncertain as to which patients will follow the metaplasia, dysplasia and carcinoma sequence.

Surveillance in Barrett's Oesophagus

Improvements in surveillance tools, e.g. endoscopy, augmented by ultrasonography, other imaging modalities and molecular markers may enable surveillance to become less invasive and give greater reliability in detecting disease progression.

Given the possibility that the risk of adenocarcinoma might persist even after ARP, endoscopic surveillance is still recommended. Since upper gastrointestinal endoscopy in children requires specialist facilities with provision for appropriate endoscopes, general anaesthetic and day-case arrangements, a sensitive biomarker for this condition would be particularly useful. The measurement of deletion and LOH at fragile sites may prove to be a biomarker of cancer risk in patients with BE and could play a role as an indicator of success of chemopreventive strategies in BE.

In the meantime, controversy exists regarding efficacy of screening and surveillance [73]. Some US studies have shown survival benefits in patients with BE who undergo endoscopy at least 1 year prior to diagnosis of cancer [74, 75]. Early diagnosis is thought to improve prognosis by detecting early-stage tumours and higher respectability. North American economic models suggest that screening of high-risk individuals is cost-effective as opposed to no screening [76–78]. However, one retrospective case-controlled study showed that surveillance endoscopy did not reduce the risk of death from oesophageal cancer in patients with BE [79]. They reviewed records of 36 patients who had a diagnosis of BE >6 months before diagnosis of oesophageal adenocarcinoma and subsequently died of cancer or treatment. These were matched with a control group of 134 patients who subsequently developed BE but did not die of cancer or treatment. Both these groups of patients had a similar proportion 3 cm or more Barrett's segments. The BE group had a higher prevalence of HGD at initial examination, but otherwise the two groups were similar. The age or other criteria for which surveillance should be commenced in children are yet to be determined.

A barium swallow has a limited role to play in surveillance. It may show some indirect features concomitant with BE but is not diagnostic. For example, an upper gastrointestinal contrast study can identify dysphagia as a consequence of oesophageal stricture secondary to reflux and scarring and after oesophageal atresia repair. It will also show poor oesophageal contraction and delayed oesophageal emptying.

Surveillance Recommendations

Columnar lining of the oesophagus confers a 30–40-fold increase in the incidence of carcinoma. About 50 % of cancers detected at screening endoscopies are early-stage cancers [3]. Recommendations for surveillance of BE apply to adult patients. The paucity of guidelines in children is partly because a significant proportion of children with Barrett's oesophagus does not have symptomatic reflux. In a Swedish study, 44 % patients from a random sample lacked symptoms of troublesome reflux and heartburn [80]. The natural history of asymptomatic reflux is unclear. The risk group in adults comprises of those over 40 years of age, with long-standing reflux and those with heartburn [81–83]. No such risk group for BE has been identified in children. Therefore, no definite surveillance guidelines in children have been developed. The recommenda-

tion for screening in adults, however, is yearly screening for patients with frequent reflux (several episodes per week) or chronic long-standing reflux (>5 years). If screening oesophagogastroduodenoscopy (EGD) shows no abnormality, there is no need for further screening endoscopies. When Barrett's oesophagus is identified, ongoing screening is indicated. When the endoscopic appearance is suggestive of BE or when the diagnosis is confirmed histologically, repeat endoscopy should be undertaken within 6–12 months with multiple biopsies obtained from all four quadrants at multiple levels above the gastro-oesophageal junction (GEJ).

Any macroscopic lesion is biopsied specifically in addition to the multiple other biopsies taken. A commonly practised approach is to obtain four-quadrant biopsies at 2 cm intervals [66]. The biopsy specimen should be examined by an experienced paediatric gastroenterology pathologist and classified as carcinoma, high-grade dysplasia (HGD), low-grade dysplasia (LGD), indefinite for dysplasia or no dysplasia. If there is evidence of dysplasia on the initial biopsy, a repeat biopsy should be taken within a year. If the repeat biopsy is not dysplastic, the risk of progression to malignancy is believed to be low. Further surveillance biopsies in these cases can be done after 3 years or by AGA consensus, 5 years, as patients with HGD have a 30 % chance of progressing to oesophageal carcinoma [84].

Most experts would take HGD as a threshold for intensive surveillance or more aggressive treatment: definitive surgical treatment, mucosal ablation or close surveillance. Comorbidities in adults influence the mode of treatment. Since children tend not to have comorbid factors, close surveillance is more readily undertaken. If mucosal ablation is undertaken, the follow-up should include biopsies of the entire area of prior Barrett's mucosa at intervals appropriate for the prior grade of dysplasia until three consecutive biopsies are normal. Various surveillance protocols in patients with HGD have been proposed (Table 73.3).

The role of surveillance for LGD is less certain as the risk of LGD progressing to carcinoma is less well defined. The recommendation of the American Society for Gastrointestinal Endoscopy (ASGE) is a repeat endoscopy at 6 months with multiple biopsies. If LGD is confirmed, it would seem reasonable to undertake yearly surveillance endoscopy with biopsies for the duration that dysplasia persists. Oesophagitis can mask changes in the oesophageal mucosa. In a study by Hanna et al. [86], about 12 % patients with erosive oesophagitis were found to have BE after treatment of their condition. Hence, a repeat biopsy should be performed after 8 weeks of acid

Table 73.3 Surveillance protocol in dysplasia [85]

No Dysplasia	**Low grade dysplasia**	**High grade dysplasia**	Every three months for one year with 4 quardrant biopsies 1 cm apart
Every 2-3 years	Repeat endoscopy and biopsy at 1 year. If no HGD at that time, then endoscopy and biopsies every 2-3 years	If no progression to dysplasia or cancer on 2 consecutive endoscopies	6 monthly for 1-2 years

suppression therapy if the first biopsy revealed indeterminate dysplastic changes and/or acute inflammation secondary to GERD. Endoscopic brush cytology has also been proposed as a diagnostic tool [87]. The application of this technique has been limited, but with the development of more sensitive fluorescent in situ hybridization techniques, its clinical utility may improve [88]. Capsule endoscopy is a new, noninvasive technique that may eventually replace routine endoscopy. Although initial studies described high sensitivity, subsequent studies have been less enthusiastic [89, 90]. The special setup, equipment, cost implications and technical difficulties in introducing the capsule in children have limited the application of this technique in paediatrics.

New Diagnostic Techniques

Narrow-band imaging and autofluorescence imaging have been used to detect dysplastic areas. In narrow-band imaging the illuminating light is filtered into blue and green colours which have a differential absorption in blood vessels of the mucosa and the subepithelial layer allowing better to visualization of the mucosa with a high-resolution endoscope [91–93]. In one study the specificity of narrow-band imaging was found to be 98.7 % [94]. The autofluorescence technique uses blue light to detect fluorescence from oesophageal lining. Areas of dysplasia do not have the normal fluorescence and appear dark red. One study using autofluorescence identified dysplasia in 100 % cases, but there was a 40 % false-positive rate [95]. Chromoendoscopy, still used in some places, relies on the observation that methylene blue binds to areas of intestinal metaplasia but not to areas of high-grade dysplasia or cancer. Prospective studies have not found chromoendoscopy to be superior to four-quadrant biopsies in the detection of dysplasia [96–98]. All these methods gain in utility with larger areas of dysplasia. Different imaging techniques are used to establish changes in smaller areas. Optical coherence tomography uses light to create interference patterns to detect intestinal metaplasia [99]. Laser confocal microscopy can magnify the mucosa and actually image the cellular structures. In a study of 63 patients, this technique showed an accuracy of 94 % in detecting neoplasia [100]. Spectroscopic instruments to assess the optical properties of light have been combined to allow improved visualization and characterization of the mucosa. All these imaging techniques and systems are potentially attractive but at this stage are not feasible for routine clinical investigations at this time (Table 73.4).

Search for a Reliable Biomarker

The availability of a sensitive and specific biomarker would assist in the surveillance and screening of BE. Various nuclear DNA content abnormalities like aneuploidy, tetraploidy and loss of heterozygosity of genes like p16 and p53 have some value in predicting cancer risk in patients with BE. Flow cytometry on fresh frozen specimens is used to demonstrate aneuploidy and tetraploidy. There is virtually no risk of cancer development in the absence of aneuploidy and tetraploidy on flow cytometry [101], whereas the presence of either of these increases the risk of cancer. Unfortunately, these techniques have limitations due to the number and size of biopsies required. Similarly, the loss of heterozygosity of

Table 73.4 Role and reliability of various imaging techniques [84]

Technique	Useful in detecting	Reliability	Drawback
Narrow-band imaging	Dysplasia	Up to 98 %	
Autofluorescence	Dysplasia	100 %	40 % false positive
Chromoendoscopy	Metaplasia	Uncertain (not superior to four-quadrant biopsies)	
Laser confocal microscopy	Neoplasia	94 %	

p16 and p53 is indicative of 16-fold increased risk of cancer [102], but these techniques have only been used in specially processed tissues, and hence clinical validation is required before they can be used in standard practice. Multiple biomarkers including markers of cell immortalization, loss of apoptotic control, angiogenesis, cell proliferation and cell cycle abnormalities have been proposed, but none have been validated in clinical studies.

Ongoing search for new markers has resulted in the discovery of sialyl Lewis^a, LewisX, *Aspergillus oryzae* Lectin (AOL) and Wheat-Germ Agglutinins. These can be studied in formalin-fixed tissues. Cyclin A is a marker of cell proliferation and correlates with the degree of dysplasia. It can be assessed using immunohistochemistry techniques. DNA content abnormalities [103] have been known to be important in disease progression and can be measured by flow and image cytometry [104]. The role of p53 in the development of OAC is well known and inactivation of this gene plays a vital part in development of OAC.

Changes in glycan expression occur in the development of OAC. Most genes which influence glycan pathways do so via Lewis antigens (Le) which are also known to be altered in many other malignancies [105–107].

Bird-Lieberman et al. [108] have previously shown that expression of Le antigens, sialyl Lewis^a and LewisX correlates with the degree of dysplasia in BE. They have, in a different study, also confirmed decreased binding of lectins (specific glycan-binding proteins) like Wheat-Germ Agglutinin (WGA) and *Aspergillus oryzae* Lectin (AOL) in progression of BE to EA. sLe^a and LeX are new markers which may help to predict the behaviour of BE in the future.

A more recent study by Bird-Lieberman et al. [109] suggests an 11-fold increase odds of progression to HGD or cancer if LGD already existed in BE. They have proposed a three-biomarker panel which includes DNA ploidy, sLe^a and AOL abnormalities, to ascertain the likelihood of disease progression. In their study of 89 patients who developed cancer between 1993 and 2005, cyclin A, p53 and WGA abnormalities did not show a significant trend towards disease progression. The outcome of HGD and OAC was similar based on the above markers, with the exception of p53 expression which was predictive of progression from BE to OAC. They have proposed a clinical algorithm; if ≤1 biomarker (of AOL, aneuploidy or LGD) is abnormal, a surveillance protocol should be followed. However, in the presence of ≥2 abnormal biomarkers or recognition of HGD, endoscopic ablation should be offered or recommended. This algorithm is based on limited evidence, but may serve as a guide until there is more thorough validation by further prospective studies.

Clinical application of these biomarkers and their role in detecting evolution from a premalignant condition to malignancy will play a very important role in satisfactory surveillance. While underinvestigation of the high-risk patients can result in failure to recognize disease at an early stage, over-investigation has definite cost and resource implications.

Treatment Options

Photodynamic therapy has been shown to reduce cancer risk in BE. In a prospective study, photodynamic therapy using sodium porfimer and photoradiating balloons decreased the risk of cancer by 50%. It also eliminated HGD in 78% of patients [110]. Photodynamic therapy with 5-aminolevulinic acid has been successful in eliminating HGD and early carcinoma but may cause hypotension, and there has been one report of a patient death [111]. Thermal ablation using laser produces deep tissue injury. Argon or multipolar coagulation devices produce similar results. Multipolar coagulation has been used to treat LGD and non-dysplastic BE with success rates of up to 90% after multiple applications. Argon plasma coagulation at high power output has been used to treat HGD and small cancers [112, 113].

Oesophageal adenocarcinoma can be treated by surgical or endoscopic ablation. Endoscopic ablation decreases the risk of cancer within Barrett's mucosa and is always done in combination with acid suppression treatment. This procedure involves endoscopic identification of

dysplastic areas which are then resected. Endoscopic surveillance can miss 43 % of early cancers by the time a diagnosis of cancer is made by which time it may have already metastasized [114]. However, the risk of metastatic cancer when the initial lesion is intramucosal carcinoma may be as low as 4 %, especially if there is no mucosal involvement [115]. Surgery for oesophageal adenocarcinoma can be carried out using the traditional transhiatal approach or using minimally invasive laparoscopic or thoracoscopic techniques. Minimally invasive techniques have a complication rate of up to 32 % similar to the conventional transhiatal approach [116]. Vagal-sparing oesophagectomy with colonic replacement has been described but is not popular in the adult population. A recent retrospective study comparing the long-term mortality of 200 patients with HGD treated with photodynamic therapy and mucosal resection compared with surgical resection found similar mortality between the two groups at a 5-year follow-up [117]. While the results of two forms of treatment are similar, the decision of the mode of treatment may be made according to the expertise and facilities available.

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Part XIII

Assessment of GE Reflux

GERD: History and Examination

74

Gigi Veereman-Wauters

Abbreviations

CMA	Cow's milk allergy
ESPGHAN	European Society of Pediatric Gastroenterology, Hepatology and Nutrition
GERD	Gastroesophageal reflux disease
NASPGHAN	North American Society of Pediatric Gastroenterology, Hepatology and Nutrition

A careful history and physical examination remain the basis of sound medical practice. The symptoms and signs leading to a differential diagnosis that includes gastroesophageal reflux disease (GERD) vary with age. History needs to be specific to reveal known symptom associations. Physical examination should include feeding or behavioral observation when complaints indicate problems in those areas.

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History

In the case of infants and young children, history is taken from the parents or caregivers. Attention should be paid to the child's description of the problem as soon as she or he can express her- or himself. Toddlers are able to indicate pain and provide a limited description. From the age of 5 or 6 years old, the history should definitely be taken from both the caregivers and the child. Neurologically disabled children remain largely dependent on their caretakers for a history, by proxy. In such cases, it can be important to talk with the different caregivers involved as at least a part of the day is often spent in an institution. Careful history taking is time consuming and is better done initially since it will be the basis for the differential diagnosis and plan. It also allows the physician to meet the patient and the family and to gather a sense of the social and familial setting.

A general history includes information about gestation, birth, perinatal events, prior medical conditions, medication, allergies, developmental milestones, and growth. A percentile chart for weight, length, and head circumference should *always* be part of the patient's chart.

Based on the recently published global evidence-based consensus on the definition of GERD in the pediatric population [1], history should aim at discovering esophageal and extraesophageal symptoms. Symptoms suggestive of GERD and reported

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by the parents in young children (up to 8 years) or in neurologically compromised patients include excessive regurgitation, feeding refusal, choking, gagging, coughing, sleep disturbance, and abdominal pain. Although excessive crying is often attributed to GERD and treated accordingly, there is no evidence to support the link between excessive crying in the infant and GERD. Studies in infants treated with proton pump inhibitors fail to demonstrate an effect on crying despite effectively treating acid reflux [2, 3]. Older children are able to report symptom associations that are typical for GERD such as heartburn and epigastric pain. According to the consensus [1], extraesophageal symptoms such as dental erosion and dystonia suggestive of Sandifer's syndrome are definitely associated with GERD. The association of respiratory symptoms, bradycardia, and apnea are considered possibly associated with GERD.

The changing pattern of symptoms with age is represented in Table 74.1. In the youngest age group, regurgitation and vomiting are more prevalent. In adults, epigastric pain and heartburn are typical symptoms. In an attempt to facilitate a symptom-based diagnosis of GERD, specific questionnaires have been developed and validated [4, 5]. However, their sensitivity and specificity is too low to reliably make a diagnosis of GERD, suspect complications, or predict response to therapy [6].

Finally, as always, a thorough system history should never be omitted since symptoms suggesting GERD are nonspecific and the differential diagnosis is broad. The physician should exclude symptoms caused by allergic, infectious, neurological, urinary tract, respiratory, cardiac, or psychosomatic conditions. Warning signals in a vomiting infant or child should lead to immediate appropriate action to exclude diagnoses other than GERD, especially increased intracranial pressure. Bilious or hemorrhagic vomiting, forceful or sudden vomiting, altered consciousness, lethargy, seizures, and severe failure to thrive are warning signals. These situations are more of the exception than the rule. The physician should remain alert for exceptions but be well aware that uncomplicated GERD is a common condition.

Another frequent condition is food allergy, specifically cow's milk allergy (CMA) in infants.

Table 74.1 Symptoms of GERD according to age categories

Symptoms	Infants	Children	Adults
Gastro			
Vomiting	++	++	+
Regurgitation	++++	+	+
Excessive crying	+++	+	–
Food refusal	++	+	+
Failure to thrive	++	+	–
Abnormal posturing	++	+	–
ALTE	+	–	–
Persisting hiccups	++	+	+
Respiratory			
Aspiration	+	++	+
ENT	+	++	+
Stridor	+	++	-
Chronic asthma	–	++	+
Varied			
Heartburn	?	++	+++
Epigastric pain	?	+	++
Chest pain	?	+	++
Dysphagia	?	+	++
Dental erosions	?	+	+
Hoarseness	?	+	+
Vocal problems	–	+	+
Stenosis	–	+	+

CMA and GERD both cause regurgitation and vomiting. These conditions may coexist or mimic each other. Symptoms should be reevaluated after adherence to an exclusion diet.

The most recently published guidelines by a joint committee of experts from NASPGHAN and ESPGHAN conclude that in infants and toddlers, there is no symptom or symptom complex that is diagnostic of GERD nor one which predicts response to therapy. However, in older children and adolescents, as in adult patients, history and physical examination may be sufficient to diagnose GERD, if the symptoms are typical [6].

Family History

The physician should know about chronic and congenital conditions in the family. History of gastrointestinal surgery should be specified.

Hiatal hernia or other congenital abnormalities can be inherited [7]. In some cases, GERD is familial [8]. A history of atopy in first-degree relatives is considered a high risk for CMA in infants and guides diagnosis and therapy.

Physical Examination

A careful physical examination by system is mandatory for each patient. Vital signs including blood pressure, weight, height, and head circumference should be charted. Developmental stage and neuromotor skills should be noted. Dysmorphic features may be the clue to a genetic disorder. Eczema suggests allergy. GERD does not cause any specific clinical sign. Accompanying signs may be dystrophy, dental or ENT abnormalities, wheezing or bronchial spasms, dystonia, and abnormal posturing in the case of Sandifer syndrome. The history (symptoms) and findings by physical examination (signs) contribute to the differential diagnosis.

Feeding observation is an extension of the physical examination. A skilled feeding therapist is frequently involved for this type of observation. Oral reflexes, signs of oral aversion, and swallowing can be assessed using specific scales such as the NOMAS [9].

In conclusion, although many tests are available for the diagnosis of GERRD and related complications, the care of an infant or child with possible GERD should always start with a good history and complete physical examination. Symptoms and signs of GERD are nonspecific. In other words, history and physical examination will generally give a pointer towards, but not be completely sufficient to make a diagnosis of, GERD, except in adolescents with heartburn. The physician should always be alert and have a differential diagnosis in mind. It is based on the critical first step of assessing signs and symptoms that further tests would be necessary – generally history will suffice. Each infant or child is unique and should be assessed and cared for as such. The risk is real that a patient enters a protocol based on a far too limited history and no physical examination.

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GER: The Place of pH Testing

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Introduction

Gastroesophageal reflux (GER) is the involuntary passage of gastric contents into the esophagus. GER is a physiological event several times a day in every individual, particularly after meals. Most reflux episodes are asymptomatic, brief, and limited to the distal esophagus.

The knowledge that esophageal pH measurement may be of clinical importance started with the observation that a drop in esophageal pH below 4.0. may cause heartburn [1, 2, 3]. This historical observation points out one of the major pitfalls of pH monitoring: the cutoff of "pH 4.0" was defined to separate reflux causing "heartburn" from reflux causing "no heartburn." The first clinical tests were performed in the early 1960s by Miller [4, 5, 6]. The commercialization of esophageal pH monitoring devices in the 1980s changed the work-up of GER substantially. It took many years to discover advantages but also pitfalls of pH monitoring.

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The Hardware

Purchase costs, system abilities, costs in use, number of measurements, and durability of the material are factors to consider before purchasing equipment. Of importance for pediatric use is a time indication on the display of the recording device (i.e., the number of data recorded, the real time and duration of the investigation) and the protection of event marker(s) to avoid erroneous use by the child. A system should refuse to work if it has not been calibrated properly. One of the advantages of pH monitoring is the possibility of obtaining an ambulatory recording, even in young children. The device should be as small and light as possible.

The utility of wireless technology to measure GER has been validated in several studies, with improvements over catheter-based pH monitoring in tolerability, accuracy, and sensitivity. The major advantage of the wireless capsule is the possibility to allow prolonged pH recording in more physiologic conditions. The capsule sloughs off the wall of the esophagus in 7–10 days and passes out of the body naturally. However, data in children are still limited. Recently, a new technique (Restec®) has been developed. It is a new antimony-based technologically using short pharyngeal electrodes and is indicated in patients with extraesophageal symptoms such as chronic coughing.

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pH sensors or "electrodes" exist in several forms, of which the two most popular are glass and antimony. Ion-sensitive field effect pH electrodes (ISFET) are modified field effect transistors (they are frequently used in impedance catheters). Clinical studies require a pH sensor that is both affordable and reliable. Electrodes should have an internal reference, avoiding all the technical problems due to the external reference electrode.

Reproducibility

Data obtained with a glass electrode correlate poorly with data obtained using an antimony electrode. In other words, normal ranges obtained with glass electrodes cannot be used for recordings with antimony electrodes. Whatever the type of electrode chosen, each center should preferentially use one device and one type, or a limited number of different electrodes. Data on reproducibility of pH monitoring vary from fair to poor. However, data on the reproducibility of all investigations for GER are poor, probably at least in part due to the day-to-day variability.

Location of the Electrode

The exact esophageal location of the pH electrode is of critical importance regarding the number and duration of acid reflux episodes recorded. The closer the electrode is located to the lower esophageal sphincter (LES), the more acid reflux episodes will be detected.

The Cutoff of pH 4.0

Esophageal pH monitoring is often considered as an investigation technique studying esophageal motility, which it obviously does not. In fact, esophageal pH metry does even not measure GER. The technique simply measures changes in esophageal pH, not GER. pH 4.0 may be an appropriate cutoff for heartburn, but it has not been validated in patients with respiratory symptoms caused by GER. Over time, many attempts have been proposed in literature to use other cutoff values than pH 4.0. Every cutoff value has the disadvantage that a value just above is considered normal and a value just below is considered abnormal. Therefore, the "oscillatory index," which is an index measuring the risk for erroneous interpretation, has been developed. Although the reflux index (the % of time with a pH <4.0) was not, the "area below pH 4.0" (taking into account the acidity of the reflux episode) has been shown to be related to esophagitis.

Indications

The main indications for esophageal pH monitoring are (1) clinical and laboratory research; (2) clinical procedure to diagnose acid reflux, especially in children presenting with atypical GER manifestations; and (3) the evaluation of the efficacy of anti-reflux medication [7].

Esophageal pH monitoring measures per definition acid reflux. Impedance measures acid, weakly acid, and weakly alkaline reflux. Although impedance measures many more reflux episodes than pH monitoring, the question remains if it is clinically important to measure "more" reflux. The technique of impedance is much more expensive (cost of devices and electrodes), and time-consuming for interpretation, than pH monitoring.

Esophageal pH monitoring will detect the number and duration of acid reflux episodes. Today, the role of weakly acid or nonacid reflux is still not clearly demonstrated. Weakly acid reflux has been shown to be related in time to symptoms. However, a causal relation has not been demonstrated, and there are no therapeutic trials to confirm this hypothesis. Thus, the question remains if it is clinically relevant to demonstrate that weakly acid reflux is more frequent than acid reflux or if the "association in time" is as well demonstrated for acid reflux. Moreover, especially in young infants, up to

25 % of the episodes with presence of acid in the esophagus are only detected with pH monitoring and not with impedance because there is no apparent bolus movement. In other words, since impedance recording includes pH monitoring, impedance will detect more reflux than pH monitoring. The question is: is it clinically relevant to detect more reflux episodes?

The limited therapeutic options are another reason to prefer pH monitoring to impedance in daily clinically routine. Therapeutic efficacy has only been demonstrated for dietary and positional treatment and for acid-blocking medication. It can be questioned if it is relevant to measure reflux that is obviously acid or if the therapeutic options are limited to reducing gastric acid.

Because today only acid reflux has been shown to cause symptoms (heartburn), and because medical therapeutic options are limited to reducing acid reflux but not reflux per se, a diagnostic tool measuring "acid reflux" should still be considered as the "reference diagnostic tool."

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pH and Impedance Measurements in Infants and Children

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Why Monitor the pH and/or Impedance in the Esophagus?

Gastroesophageal reflux (GER) is the involuntary passage of gastric contents into the esophagus. GER is a physiological event occurring in every individual several times during the day, particularly after meals. Most reflux episodes are asymptomatic, brief, and limited to the distal esophagus. GER may be a primary gastrointestinal motility disorder but may be secondary to other conditions, such as cow's milk protein allergy. According to recent literature, cow's milk protein allergy is a frequent cause of GER during infancy [1, 2]. This review will discuss both the advantages and disadvantages of pH and impedance techniques to measure GER.

The idea that pH measurement in the esophagus may be of clinical importance started with the observation that acid perfusion-induced heartburn coincides with a fall of intraesophageal pH below 4.0 [3]. This simple historical observation points out one of the major pitfalls of pH monitoring: the cutoff of "pH 4.0" was defined to separate reflux causing heartburn from reflux causing no heartburn. However, "heartburn" is only one of the indications for pH monitoring. In other words, pH 4.0 may be an appropriate cutoff for heartburn, but it has not been validated in patients with respiratory symptoms caused by GER. Esophageal pH monitoring is often considered as an investigation technique studying esophageal motility, which it obviously does not. In fact, esophageal pH metry does not even measure GER. The technique simply measures changes in esophageal pH, not GER. The commercialization of esophageal pH monitoring devices in the 1980s changed the workup of GER substantially. It took many years to discover advantages but also pitfalls of pH monitoring.

The first clinical tests were performed in the early 1960s by Miller [4]. Electronic technology has profoundly changed the practice of medicine, principally through its ability to monitor, record, and analyze large volumes of data. The introduction of computers has provided physicians with powerful tools to identify elusive and intermittent disorders, such as GER disease (GERD). As a consequence of this technical evolution, measurement of the impedance in the esophagus has become possible.

The basic principle of impedance recording is identical to pH monitoring: registration of esophageal events with a probe placed transnasally and connected to a recorder. Impedance allows the detection of the frequency, the esophageal height, and duration of reflux episodes, independent of the pH of the refluxate. The term "intraluminal impedance monitoring" is preferred because of

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the concurrent measurement of impedance from multiple intraluminal recording segments. The method allows detection of GOR based on changes in electrical resistance to electrical current flow between two electrodes, when a liquid and/or gas bolus moves between them (Table 76.1: GER as measured by intraluminal impedance monitoring). Impedance detects GER if there is a sequential orally progressing drop in impedance to less than 50 % of baseline values starting distally (3 cm above the lower esophageal sphincter) and propagating retrogradely to at least the next two more proximal measuring segments. According to the corresponding pH change, impedance-detected reflux can be classified as acid if the pH falls below 4 for at least 4 s or, if pH was already below 4, as a decrease of at least 1 pH unit sustained for more than 4 s. Weakly acidic reflux is defined as a pH drop of at least 1 pH unit sustained for more than 4 s with basal pH remaining between 7 and 4. Reflux is considered to be weakly alkaline when there is impedance evidence of reflux but the pH does not drop below 7 [5, 6]. According to literature, the number of weakly acid reflux episodes differs substantially (Table 76.2). In many studies, weakly alkaline and weakly acidic reflux are grouped together as "nonacid reflux." Intraluminal air (which has a very low electrical conductivity) provokes a rapid and pronounced rise in impedance [5].

The main indications for esophageal pH monitoring are (1) clinical and laboratory research; (2) clinical procedure to diagnose acid reflux, especially in children presenting with atypical GER manifestations (Table 76.3: symptoms according to age); and (3) the evaluation of the efficacy of treatment of GERD on the frequency and duration on the presence of acid in the esophagus [7, 8]. Intraluminal impedance (measuring flux of ions) will measure more events than measurements of drops in esophageal pH, since not all reflux is acid.

Table 76.1 Definition of types of gastroesophageal reflux (GER) detected by intraluminal impedance

Liquid GER: drop in impedance to less than 50 % of baseline values
Acid GER: pH falls below 4 for at least 4 s or, if pH was already below 4, decreases by at least 1 pH unit sustained for more than 4 s
Nonacid reflux: weakly acidic and weakly alkaline GOR
Weakly acidic reflux: pH drop of at least 1 pH unit sustained for more than 4 s with basal pH remaining between 7 and 4
Weakly alkaline: pH does not drop below 7
Gas reflux: rapid and pronounced rise in impedance

Hardware and Software: Pediatric Needs

The Device

Purchase costs, system abilities, costs in use, number of measurements, and durability of the material are factors to consider before purchasing equipment. Impedance equipment is considerably more expensive than pH metry devices. Of importance for pediatric use is a time indication on the display of the recording device (i.e., the number of data recorded, the real time and duration of the investigation) and the protection of event marker(s) to avoid erroneous use by the child [8]. A system should refuse to work if it has not been calibrated properly.

There is no difference between a device for pH or impedance recording: it is a "box" that stores data in memory; at the end of the recording, the device needs to be connected to a computer to read out the stored data. One of the advantages of pH and impedance monitoring is the possibility of obtaining an ambulatory recording, even in young children. The device should be as small and light as possible. For pH metry, devices no larger than a credit card, although of course a little thicker, are now commercially available.

The utility of wireless technology for GER diagnosis has been validated in several studies, with improvements over catheter-based pH monitoring in tolerability, accuracy, and sensitivity, as well as the ability to record periods both off and on therapy with proton pump inhibitors in a single study [9]. The major advantage of the wireless capsule is the possibility to allow prolonged pH recording in more physiologic conditions. The capsule sloughs off the wall of

Table 76.2 Number of reflux episodes (total and weakly acid) recorded by impedance in children

Author (references)	Indication	N° children	N° R Ep impedance	N°R Ep imp/ patient	% weakly acid R Ep
Mattioli et al. [17]	Typical and atypical GOR	50	2922	58.4	<1 year: 53 %
					>1 year: 49 %
Peter et al. [18]	Tube feeding	16	1152 (esophageal)	72	?
			1952 (gastric)	122	?
Del Buono [19]	Neurologically impaired	16	425	26.6	56 %
Lopez Alonso et al. [20]	Preterm	7	281	40.1	46 %
Lopez Alonso [21]	Preterm	21	1491	71	73 %
Condino et al. [22]	GER disease	34	1890	55.6	53 %
Condino et al. [23]	Asthma	24	1184	197.3	51 %
Omari et al. [24]	Healthy preterm	10	89	8.9	?
Corvaglia et al. [25]	Healthy preterm		1055		56 %
Wenzl et al. [26]	Regurgitation term infants	14	1183	84.5	55 %
Corvaglia et al. [27]	Preterm with regurgitation	5	316	63.2	78 %
Del Buono et al. [28]	Effect Gaviscon®	20	747	37.3	69 %
Wenzl [29–31]	Physiological apnea	22	364	16.5	89 %
Peter et al. [32]	Pathological apnea	21	524	24.9	?
Mousa et al. [33]	Apnea, ALTE	25	1211	48.4	49 %
Rosen et al. [34]	CRD	28	1822	65.1	45 %
Thilmany [35]	CRD	25	3235	129.4	? (“low”)

the esophagus in 7–10 days and passes out of the body naturally. However, data in children are currently limited [10].

The pH and Impedance Electrode

pH sensors or “electrodes” exist in several forms, of which the two most popular are glass and antimony. Ion-sensitive field effect pH electrodes are modified field effect transistors. Clinical studies require a pH sensor that is both affordable and reliable. Glass electrodes with an internal reference are “the best” but are expensive and have a rather large diameter (3.0–4.5 mm) [11, 12]. Although the passage of such an electrode through the nostrils of a baby is, most of the time, technically possible, it does not mean that it is well tolerated and that it is the best option.

Owing to their smaller diameter, antimony (2.1 mm) or glass microelectrodes (1.2 mm) are preferable in infants. Antimony electrodes also exist with a diameter of about 1.5 mm for use in premature babies; these electrodes are too flexible for use in older babies. Glass electrodes have only one pH sensor. Antimony electrodes with multiple pH sensors may help to detect alkaline reflux episodes, although measurement of esophageal pH is not recommended to detect alkaline reflux [13]. Antimony electrodes with two sensors can also be helpful to evaluate the therapeutic efficacy of acid-reducing medication: the esophageal sensor measures the incidence of acid reflux, while the gastric sensor measures efficacy of the medication. Antimony is only poorly resistant to gastric acid, but the fact that acid should be reduced or minimalized in these patients reduces the impact of this shortcoming. Thus, “Bilitec” (a technique measuring the presence of bile in the refluxed material) and non-pH-dependent techniques such as impedance offer much more benefits to measure nonacid reflux compared with using pH electrodes with multiple electrodes.

Table 76.3 Symptoms of gastroesophageal reflux disease according to age

Symptoms/signs	Infants	Children	Adults
Vomiting	++	++	+
Regurgitation	++++	+	+
Heartburn	?	++	+++
Epigastric pain	?	+	++
Chest pain	?	+	++
Dysphagia	?	+	++
Excessive crying/irritability	+++	+	–
Anemia/melena/hematemesis	+	+	+
Food refusal/feeding disturbances/anorexia	++	+	+
Failure to thrive	++	+	–
Abnormal posturing/Sandifer's syndrome	++	+	–
Persisting hiccups	++	+	+
Dental erosions/water brush	?	+	+
Hoarseness/globus pharyngeus	?	+	+
Persistent cough/aspiration pneumonia	+	++	+
Wheezing/laryngitis/ear problems	+	++	+
Laryngomalacia/stridor/croup	+	++	–
Chronic asthma/sinusitis	–	++	+
Laryngostenosis/vocal nodules problems	–	+	+
ALTE/SIDS/apnea/desaturation	+	–	–
Bradycardia	+	?	?
Sleeping disturbances	+	+	+
Impaired quality of life	++	++	++
Esophagitis	+	+	++
Stenosis	–	(+)	+
Barrett's/esophageal adenocarcinoma	–	(+)	+

+++ very common, ++ common, + possible, (+) rare, – absent, ? unknown

Glass microelectrodes and, historically, also antimony electrodes need an external cutaneous reference electrode, which may cause erroneous measurement resulting from transmucosal potential differences. If the environmental temperature is high or the patient sweats a lot, the conductivity of the contact gel will change, resulting in a less accurate conduction of the electric potential. Antimony electrodes with a diameter of about 2.0 mm containing an internal reference electrode have been developed, providing adequate results. This electrode is accurate, thin, flexible, and easy to place in the esophagus and has become standard. Data obtained with a glass electrode correlate poorly with data obtained using an antimony electrode [14]. In other words, normal ranges obtained with glass electrodes cannot be used for recordings with antimony electrodes. Whatever the type of electrode chosen, each center should preferentially use one device and one type or a limited number of different electrodes.

Prior to each study, an in vitro two-point calibration must be carried out. The electrode and reference are placed in two buffer solutions (usually pH 1.0 and 7.0; for antimony pH 4.0 and 7.0) at either room or body temperature until stabilization is reached. This calibration should be repeated on return of the patient to rule out electrode failure and to check for slow pH drift. A drift of less than 0.5 pH over the 24-h period is acceptable. Calibration needs to be corrected according to both room and body temperatures.

Both the device and the electrodes for impedance testing are considerably more expensive than those used for pH metry. The impedance electrode also has one or two antimony sensors to

measure pH and rings (generally 6) to measure impedance. In older patients, the pH electrode at the tip of the catheter measures gastric pH, whereas the other pH antimony sensor measures esophageal pH.

Location of the Electrode

The exact esophageal location of the pH electrode is of critical importance regarding the number and duration of acid reflux episodes recorded. The closer the electrode is located to the lower esophageal sphincter (LES), the more acid reflux episodes will be detected [15, 16]. In adults, the electrode is, by consensus, positioned 5 cm above the proximal border of the LES. Also in adults, determination of the position of the LES by means of a standard stationary esophageal manometry study is generally regarded as the optimum method for pH probe localization [12]. In children, several other methods have been proposed to determine the location of the electrode: fluoroscopy, calculation of the esophageal length according to Strobel's formula (distance from the nose to the cardia = 5 + 0.252 [length in cm]), and endoscopy. Ideally, as in adults, the electrode should be sited in reference to the manometrically determined LES. However, this has several inconveniences: (1) manometry in infants and children is time consuming, rather invasive, or at least unpleasant and (2) this method has the inconvenience that the electrode is located at a fixed distance to the LES, whereas the length of the esophagus increases from less than 10 cm in a newborn to over 25 cm in an adult. Moreover, manometry cannot be performed in all centers. Therefore, the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition Working Group recommended the use of fluoroscopy to locate the electrode [8]. The radiation involved is minimal, and the method can be applied in each center. As the tip of the electrode moves with and during respiration, the tip should be positioned in such a way that it overlies the third vertebral body above the diaphragm throughout the respiration cycle. Dislocation by a curled electrode is also prevented with fluoroscopy. If the pH device is exposed to X-rays, the data and calibration may be erased.

For impedance it is also relevant to know the location of the impedance sensors, since the esophageal height of reflux episodes is considered one of the advantages of impedance.

Impedance: The Technique

Experience with pH monitoring has shown the pitfalls of an arbitrary cutoff limit such as pH 4.0. A similar comment can be made for impedance: the automated analysis considers only a drop of impedance of 50 % or more as a reflux episode. However, it is likely that a drop of 49 % also can be attributed to reflux. Although impedance interpretation necessitates a manual analysis, the relevant question remains what level of decrease in impedance is needed to be considered as a reflux episode? A drop in impedance is not related to the volume of the refluxate. The multiple impedance rings allow the height of the reflux episode to be identified. If pH monitoring is performed with a probe with multiple pH sensors, it is also possible to determine the height of the refluxate. The major difference between both techniques is restricted to the detection of nonacid reflux. As a consequence, another fundamental questions arises: what is the clinical relevance of nonacid or weakly acid and alkaline reflux?

Patient Preparation

Other than fasting, no special patient preparation is required for pH monitoring. The patient should fast for at least 3–5 h before the study, depending on the age, to avoid nausea and vomiting. If the child is able to communicate, it is important to reassure the child at the beginning of the study and explain what will happen. The child should understand that the passage of the catheter through nostrils and pharynx is uncomfortable,

but after the first few swallows, it will feel better. To facilitate insertion, a spray containing silicone can be placed on the electrode (but not on the pH sensor!), and/or the mucosa of the nostrils can be sprayed with a topical anesthetic. Sedation should not be used because the sedative interferes with swallowing and influences LES pressure.

Histamine$_2$ (H^2) blockers and proton pump inhibitors should be stopped at least 3 or 7 days, respectively, before a diagnostic pH monitoring (except when the investigation is performed to evaluate the acid-blocking effect of the drug). Antacids are permitted up to 6 h prior to the start of the recording. Prokinetics should be stopped at least 48 h before the pH monitoring [15]. Whether acid-suppressing medications decrease reflux events or only change the pH of the reflux events has been insufficiently validated with impedance. This issue is one of the priority areas for research with impedance.

It is best not to start a pH metry study the same day that an upper gastrointestinal tract endoscopy is performed because the sedation, fasting, and inflated air may be confounders. It is best to start pH metry at least 3 h after a barium swallow or radionuclide gastric or esophageal studies.

Patient-Related Influencing Factors: Recording Conditions

Feeding, position, and physical activity are examples of patient-related factors influencing reflux events. Patient-related factors that possibly influence the results of reflux investigations remain a controversial topic [8, 15]. The answer to the fundamental question regarding whether patient-related factors should be minimized and standardized is difficult and necessarily ambiguous. If the reflux investigation is performed as part of a diagnostic workup in a patient, it is interesting to undertake the study during normal daily life. On the other hand, if the reflux investigation is performed as part of a clinical research project, recording conditions should be standardized. Standardization of recording conditions inevitably causes a loss of patient-specific information.

Duration of the Recording

The duration of the recording should be as close as possible to 24 h and at least 18 h, including a day and a night period both for pH and impedance measurements [8, 36, 37]. If pH monitoring is performed for diagnostic purpose, there is no indication for short-duration pH tests (e.g., Tuttle and Bernstein tests, 3-h postprandial recording). The first reports on the clinical use of pH monitoring concerned esophageal tests of short duration. Tuttle and Grossman developed the "standard acid reflux test" [38]. This test was modified by Skinner and Booth [39] and Kantrowitz and colleagues, [40] demonstrating that pH tests can contribute to define abnormal GER. The Tuttle test was reported to have a sensitivity of 70 % [41]. However, after great initial enthusiasm for this test, criticism was overwhelming. The test is unphysiologic in requiring intragastric instillation of acid and various artificial maneuvers to raise intragastric pressure. In the early 1980s, it was reported that the false-positive rate might be as high as 20 % and false-negative rates as high as 40 % [42–44]. Bernstein and Baker demonstrated, in 1958, that heartburn could be provoked by infusing diluted hydrochloric acid into the esophagus in susceptible individuals [45]. This test was reported to be 100 % positive in heartburn patients [46]. A modified Bernstein test was used to illustrate the relationship between GER and apnea and stridor and between nonspecific chest pain and GER [47, 48]. Provocative testing can be used in particular conditions to demonstrate the relationship between GER and specific symptoms such as bradycardia in relation to the presence of acid in the distal esophagus. However, provocative testing has the inconvenience that the investigation conditions are unphysiologic, which likely explains discrepancies reported in the literature. For instance, Ramet and colleagues showed prolongation of the R-R interval on ECGs in infants during provocative testing with instillation of acid in the esophagus [49], whereas other investigators could not reproduce these findings in 24-h

recordings under more physiologic conditions [50, 51].

There is now substantial evidence that both in controls and in the majority of infants and children with classic symptoms of GERD, esophageal acid exposure is highest during the day, probably because of provocation of GER by food ingestion and physical activity. Controls have more reflux upright than supine and more reflux awake than asleep [52]. The relationship between esophagitis and nocturnal acid reflux is far from clear [53–55]. Limited experience with impedance confirms knowledge for pH monitoring: more reflux during the day (during activity) than at night (during sleep), more acid reflux during fasting, and more nonacid reflux during feeding.

The reproducibility of impedance-pH recording on two consecutive days is rather poor, especially for nonacid reflux [51]. The variability between the number of acid and nonacid reflux episodes with a second recording performed 2 days after a first recording have a high variation: 0.2–5.3 and 0.04–8.6 times the value obtained at day 1, respectively [56]. However, reproducibility of pH monitoring on two consecutive days is reported to have high correlation coefficients, ranging from 0.88 to 0.98 [57]. Applying a similar study design, Nielsen and coworkers reported an overall reproducibility of 70 % for impedance [58]. The reflux index at day 2 was 0.2–3.3 times the initially obtained value at day 1 [58].

Intraluminal impedance monitoring data can be read manually or analyzed automatically using commercially available software. Over 95 % of reflux events detected by automatic impedance-pH analysis were confirmed by two independent investigators, although they added about 33 % acid, weakly acid, and nonacid reflux episodes [59]. The agreement between investigators for reflux episodes detected by manual reading of 24-h impedance-pH tracing was only about 50 % [59]. Interobserver variability was reported much better in impedance recordings obtained in neonates during a period of 6 h [60]. The discrepancy between automatic analysis and manual reading is influenced by the preset definitions of the automatic reading: the software indicates as acid reflux only in those episodes in which the impedance falls below 50 % of baseline in two consecutive channels simultaneously with a drop in pH below 4. This means that the reflux (or "drop in impedance") should reach at least 5–7 cm above the pH channel to be detected as "acidic impedance reflux." Most pediatric centers choose to register all reflux episodes detected with the pH channels independently from the impedance reflux events. More data are needed regarding the comparison between automatic and manual reading. It is clear that more reflux episodes are detected with manual reading; however, it has not been shown that more reflux detected equates to better diagnosis. Moreover, manual reading induces human bias in the interpretation of the results. In general, "pH reflux" does last longer than "impedance reflux," or in other words, acid exposure lasts longer than bolus exposure. This observation is likely to be related to a difference in clearance time between acid and bolus exposure.

Feeding

Feeding during pH monitoring is an area of controversy. On the one hand, it seems logical to forbid the intake of acidic foods and drinks. However, many popular foods and beverages have a pH of <5.0 (e.g., cola drinks, fruit juice, tea, soup), resulting in a quite restricted diet. A too restricted diet might alter the patient's normal dietary habits in such a way that the investigation is no longer performed in physiologic conditions. Electrodes are temperature sensitive; therefore, very hot and ice cold beverages and foods (e.g., coffee, tea, ice cream) should be avoided [8]. Chewing gum or hard candy should be withheld because these increase saliva production and thereby induce swallowing and esophageal peristalsis, tending to normalize test results. This is also true for impedance recording: during periods of increased saliva production and swallowing, less reflux will occur. In older children, alcohol intake and smoking should be recorded on the diary.

In infants, it has been suggested to replace one or several feedings during pH monitoring with apple juice [55]. This solves the problem of gastric anacidity after a milk feeding. Apple juice has a pH of about 4.0, has a very rapid gastric emptying, and is not part of normal infant feeding. Although the ingestion of acid, such as a cola drink, might simulate a reflux episode, the duration of ingestion is limited to a few minutes and most of the time irrelevant in relation to 24-h data. It is also possible to eliminate these false reflux episodes with the help of a diary. Impedance (in combination with pH) recording allows much better determination of the bolus movement: from proximal to distal, as happens after a swallow, or from distal to proximal, as happens during GER.

The influence of a particular food on the frequency of acid GER episodes detected by pH monitoring might be opposite to its influence on the incidence of reflux episodes: for instance, a high fat meal provokes GER because of delayed gastric emptying [61]. Since the duration of postprandial gastric anacidity after a fatty meal is prolonged, a meal with a high fat content will result in delayed gastric emptying, and thus, less acid reflux episodes will be detected by pH monitoring [61, 62]. Postprandial GER after feedings varying in fat content is an interesting research topic for impedance. Some drugs that influence gastric emptying have a comparable effect on pH monitoring data: prokinetic drugs enhance gastric emptying, shorten the period of postprandial gastric anacidity, and prolong the periods during which acid GER can be detected. Combined impedance and pH recording may enhance understanding of the effects of various constituents of food on GER.

The impact of postprandial nonacid reflux decreases with age, since the number of feedings decreases, and with it the total duration of postprandial periods and the overall buffering effect of milk [22]. It seems logical that nonacid reflux events decrease with time elapsed from the last meal [20]. While symptom correlation (within a 5-min window) is similar between acid and nonacid reflux (25.2 % vs 24.6 %), reflux events reaching the proximal esophagus are more frequently associated with epigastric pain and burping [22].

Position

Different patterns of GER (upright, supine, combined) have been reported in adults and older children [63]. Orenstein and colleagues demonstrated that the prone sleeping position is the preferred position for infants as far as GER is concerned because crying time is decreased if compared with the supine position [64–66]. There is evidence that the prone anti-Trendelenburg 30° sleeping position reduces GER in normal subjects and patients, although the position is difficult to apply and maintain correctly (infants have to be tied up in their bed). Meanwhile, the literature on sudden infant death syndrome (SIDS) shows that infant mortality decreases if infants are put to sleep in supine position [67, 68]. The position of the infant should be recorded on the diary during reflux monitoring. The impact of position has been analyzed through combined manometry and impedance in ten healthy preterm infants (35–37 weeks of postmenstrual age): 89 reflux episodes were recorded (74 % were liquid, 14 % air, and 12 % with mixed contents) [24]. In the right lateral position, the total number of reflux episodes (as well the total as the liquid episodes) was significantly higher than in the left lateral position despite a faster gastric emptying in the right position. This finding suggests that the major pathophysiological mechanisms causing reflux episodes are inappropriate transient relaxations of the lower esophageal sphincter [24, 25].

In addition to position, the effects of formula feeding and alginate on height, frequency, and type of reflux have also been studied. Impedance confirms the efficacy of an anti-regurgitation formula on the frequency and severity of regurgitation with a trend for a more pronounced effect on nonacid reflux [26]. Although there was a trend for reflux to be less proximal, the difference was

not significant [26]. In other words, with the antiregurgitation formula tested, there was no statistically significant difference in the duration and number of acid and nonacid GER and in the height of the reflux episodes [28]. Impedance shows that alginates do not decrease the number of postprandial episodes of GER, but may marginally decrease the height of the refluxate [28].

Data Analysis

Interpretation and Parameters

Interpretation starts with a visual appreciation of the tracing, which is subjective and difficult to standardize. Nevertheless, it is of the outmost importance to look at the tracing. A progressive constant reduction in esophageal pH at the end of a feeding, which continues up to the next feed, may be suggestive for cow's milk protein allergy [69]. Parameters that are classically analyzed for pH monitoring are the total number of reflux episodes, the number of reflux episodes lasting more than 5 min, the duration of the longest reflux episode, and the reflux index (the percentage of time of the entire duration of the investigation during which the pH is less than 4.0). From all classic parameters, the acid exposure time or reflux index is the most relevant. The correlation between all four parameters is good, and they are closely related to the reflux index [70]. Results should also be automatically calculated for periods of interest, such as sleep, wakefulness, feeding, postprandial fasting, and body position. A time relation between atypical manifestations (e.g., cough, bradycardia, desaturation) and changes in pH (not necessarily a drop in pH below 4.0) should be searched for. The duration of reflux during sleep has been suggested to be a good selection criterion for reflux related to apnea in infancy (the "ZMD score") [71]. For unclear reasons, this parameter has been insufficiently validated. However, it should be noted that the response time of an antimony electrode (the time needed to reach 95 % of the exact pH) is at least 5 s. The "area below pH 4.0" is a parameter considering the acidity of reflux episodes [72], which has been shown to correlate better with the presence of reflux esophagitis than with the reflux index in children [73].

Various complex reflux scoring systems (Johnson-DeMeester composite score, Jolley, Branicki, Kaye, Boix-Ochoa scoring systems) have been developed. The majority of the parameters were developed for assessing reflux esophagitis in adults. Jolley and colleagues proposed a score for children [74]. However, there is abundant literature, both in adults and children, that not one parameter of pH monitoring (except the "area under pH 4.0") and no single symptom has a high specificity for esophagitis. Endoscopy and histology remain the gold standard to diagnose esophagitis. In marked contrast to these complex scoring systems is the simple recommendation by some investigators that the reflux index or total acid exposure time should be regarded as the most important, if not the only, variable in clinical practice [70, 72]. Scores based on symptom indices are not applicable in infants and young children.

A major interfering factor in the interpretation of pH monitoring data is the "yes" or "no" interpretation provided by a computer software: a pH of 4.01 is regarded as normal, whereas a pH of 3.99 will be considered as acid reflux. Minimal changes in esophageal pH around pH 4.0 can be at the origin of different software interpretations, although without difference in clinical meaning. The oscillatory index, a parameter measuring the time pH oscillates around pH 4.0, was developed to evaluate this risk for erroneous computer interpretation [75].

A similar comment can be made regarding impedance: a drop in impedance of 50 % is postulated to be a GER episode. However, it is very unlikely that a drop in impedance of 49, 50, or 51 % has a different meaning. Although impedance allows or more often requires a manual analysis, the relevant question that remains is why is the decrease in impedance needed to be considered as a reflux episode? The drop in impedance is not related to the volume of the refluxate. If pH monitoring were to

be performed with a probe with multiple pH sensors, it would be possible to determine also the height of the refluxate. The major difference between pH and impedance-pH monitoring is restricted to the detection of weakly acid reflux.

Normal Ranges

As for any measurement, normal ranges are mandatory. However, because there is a continuum between physiologic GER and pathologic GERD, normal ranges should be regarded as a guideline for interpretation. Reproducibility has been shown for various parameters. Intrasubject reproducibility supports the diagnostic use of continuous pH monitoring. In general, a reflux index above 7 % is considered as abnormal, a reflux index below 3 % as normal, and a reflux index between 3 % and 7 % as indeterminate. However, normal ranges were developed to separate patients at risk for esophagitis from those not at risk, which is not the major indication of the procedure. Normal ranges proposed by one group can be used by another group only if the investigations are performed and interpreted in a comparable way. This means that materials and methodology should be identical. For some individuals and in some clinical situations, it may be more important to relate "events" (e.g., coughing, wheezing, apnea) to recorded events rather than to know if the data are within the normal range. There are no normal ranges currently available for impedance.

Significantly fewer acid reflux episodes are detected using pH monitoring combined with impedance when compared to pH monitoring alone [76]. Estimates of esophageal acid exposure using pH monitoring alone were twofold higher than estimates derived using pH and impedance techniques. Of the total acid reflux episodes detected by pH monitoring alone, almost three-fourth could not be confirmed by combined pH and impedance [18]. Detection of significant numbers of "pH-only" episodes raises concerns regarding possible overestimations of acid exposure that may occur when estimates are based solely on esophageal pH monitoring.

Weakly Acid Reflux

Weakly acid reflux was previously called nonacid reflux. Up to now, there has been general consensus that investigations measuring reflux during the postprandial period (ultrasound, radiology, scintigraphy) are of limited value in the diagnosis of GER disease because of the high prevalence of GER in the postprandial period. The pH of reflux during a postprandial period is mostly above pH 4 (thus regarded as nonacid based on pH monitoring criteria). However, based on experienced obtained with impedance, there is general consensus that it is preferable to consider this type of reflux as "weakly acid" reflux.

If a nasogastric tube passes the cardia, impedance shows an increase in postprandial reflux (from 72 to 122 episodes) in preterm infants [18]. Del Buono confirmed these findings in neurologically impaired children: more than half of the reflux events are nonacidic and would therefore go undetected by conventional pH metry [19]. The number of reflux episodes, both acid and nonacid, and the median height of reflux events were increased in the subgroup that was fed through a nasogastric tube, compared to the orally fed subgroup [63]. However, the difference in GER events may well be explained by the difference in neurologic impairment between groups. In a small group of seven healthy preterm newborns receiving nasogastric milk feeding, the mean prevalence of nonacid reflux (29 episodes/24 h) was more than two times the prevalence of acid reflux (12 episodes/24 h), and about 80 % of these reflux episodes reach the proximal esophagus [20]. The same group reported in a larger series of 21 healthy premature neonates a much higher incidence of approximately 70 reflux events in 24 h; of the reflux episodes, 25 % were acid, 73 % weakly acidic, and 2 % weakly alkaline [21]. In preterm infants, weakly acidic reflux is more prevalent than acid reflux, particularly during the feeding periods [21]. In contrast, similar to healthy adults, weakly alkaline reflux

was uncommon. Most reflux events are pure liquid during both fasting and during postprandial periods; gas reflux is very rare. The majority of reflux events in asymptomatic preterms reaches the proximal esophagus or pharynx. The acid exposure related to reflux events and detected by impedance is significantly lower than the total acid exposure during 24 h [72]. Increased acid exposure could be attributable to pH-only reflux events or, less frequently, to slow drifts of pH from baselines at approximately 5 to values <4. These changes are not accompanied by a typical impedance pattern of reflux but by slow drifts in impedance in one or two channels. These findings confirm the need for the use of impedance together with pH metry for diagnosis of all GER events [21]. Conversely, Condino and coworkers report in a group of 34 infants, aged between 2 and 11 months, that the distribution or acid and nonacid reflux is almost equal: 47 % of the reflux episodes were acid and 53 % nonacid [22].

Chronic respiratory symptoms such as chronic bronchitis, wheezing, chronic cough, and infant apnea have been related to GER. A strong relationship between acid and nonacid GER and respiratory abnormalities was suggested by Wenzl et al.: in a group of 22 children presenting with repetitive regurgitation and chronic respiratory symptoms, impedance recorded 364 reflux events, of which only 11.4 % were acid [29]. Three hundred and twelve (85 %) of these reflux episodes, of which 12 % were acid, were associated with irregular breathing [73]. In a minority of these episodes (n:19), oxygen desaturations of more than 10 % occurred (3/19 or 19 % of such episodes were acid). Analysis of the polysomnographic recording showed 165 episodes of apnea, of which 30 % were associated with a reflux episode; again, the majority (78 %) of reflux episodes were detected with impedance only [29]. However, an association between pathologic central, obstructive, or mixed apnea and GER has not been convincingly demonstrated but has also not yet been well studied. Clear cutoff values discriminating normal from pathological children still need to be determined. The number of reflux events per hour (two to three events per hour) is slightly lower in normal healthy preterm infants than in premature neonates with cardiorespiratory events (four per hour) [21]. When compared with pH monitoring, impedance is a technique that will allow a more accurate determination whether apnea of short duration is a physiologic phenomenon occurring frequently in relation to an episode of GER [77]. In a group of 22 infants, 364 episodes of GER were detected with impedance [30, 31]. Visual validation records confirmed 165 apneas. Of these events, 49 (30 %) were associated with GER and 38 (77.6 %) were exclusively recorded by impedance [30, 31]. A decrease of oxygen saturation >10 % was observed in 19 reflux events recorded with impedance, of which only 3 (15.8 %) episodes were acid (pH <4.0) [30, 31]. Nineteen preterm infants (gestational age 30 weeks) presenting with apnea were studied at a mean age of 26 days (13–93 days): 2039 episodes of apnea (median: 67; range: 10–346), 188 oxygen desaturations (median 6; range 0–25), 44 bradycardias (median 0; range 0–24), and 524 episodes of GER (median 25; range 8–62) were detected [32]. The frequency of apnea in a 20-s period before and after an episode of GER was not different than the frequency of apnea not related to a reflux episode (0.19/min [0.00–0.85] versus 0.25/min [0.00–1.15]) [32]. The analysis and conclusions were identical for oxygen desaturations and bradycardias [32]. Mousa analyzed the temporal relationship between apnea and GER in a group of 25 infants presenting with an apparent life-threatening event (ALTE) or pathologic apnea [33]. A time interval as long as 5 min between apnea and reflux was considered acceptable to demonstrate a “temporal link” between the two phenomena [33]. In total, 527 apnea episodes were recorded but only 80 (15.2 %) were temporally linked to a reflux episode. Of these 80 episodes, 37 (7.0 % of the total episodes of apneas) were related to acid reflux and 43 (8.2 %) to nonacid reflux. Thus, even when considering a time interval as long as 5 min, one can conclude that a relationship between reflux and apnea is uncommon [33]. The majority of the reflux events reach the proximal esophagus or the

pharynx, both in asymptomatic preterm babies and in neonates with cardiorespiratory symptoms [21]. This lack of discernable differences between asymptomatic and diseased infants contravenes the hypothesis for macro- or microaspiration, but does not exclude hypersensitivity to reflux as a cause for respiratory symptoms.

Chronic respiratory manifestations, such as coughing and wheezing, are reported to occur in older children with reflux. Rosen and coworkers reported their experience in 28 children (mean age: 6.5±5.6 years) with chronic respiratory disease under treatment with antacid medications [34]. A total of 1822 episodes of reflux were measured with MII-pH; 45% of them were nonacid. Multivariate analysis showed a stronger association between respiratory symptoms and nonacid reflux episodes than with acid reflux episodes [34]. Also the height of the refluxate in the esophagus was related to respiratory symptoms: the higher the reflux, the stronger the association [34]. The association score between symptoms and episodes of reflux detected with impedance and pH monitoring was 35.7±28.5 and 14.6±18.9 (p=0.002), respectively [34]. However, it is not too surprising that pH monitoring detects less reflux during antacid treatment. In a series of 25 children (age 6 months to 15 years) with unexplained chronic cough, wheeze, or sputum production, data support a relation between acid GER and chronic pulmonary symptoms, but do not support a role of nonacid reflux in children with respiratory symptoms not on antacid medication [35]. Condino et al. studied 24 children with recurrent asthma and concluded that both acid and nonacid reflux occur with equal frequency in children with asthma and that most symptoms occur in the absence of a reflux event [23]. In a selected group of 22 adults, a relation between chronic cough and GER was studied by combined manometry and MII-pH [5]. Using a time frame of 2 min and symptom association probability, 69.4% of coughing episodes were considered independent of a reflux episode. When a "reflux-cough" sequence occurred, the reflux in 65% of cases was acid, in 29% weakly acid, and in 6% weakly alkaline [5]. Contradictions in the literature on the role of acid and nonacid GER in children with chronic respiratory symptoms may, in part, be explained to the fact that these studies have not considered whether reflux is primary (motility disorder) or secondary (to infection, allergy, respiratory efforts, etc.) in nature.

The use of pH alone for the detection of acid reflux is very sensitive but lacks specificity compared with MII-pH. pH alone may overdiagnose abnormal acid reflux. Also, the use of pH for the detection of weakly acid reflux has poor sensitivity [78].

pH Monitoring and Other Investigations

Many different techniques to evaluate GER exist, focusing on different aspects, such as postprandial reflux (scintiscan, barium swallow, ultrasonography), histologic abnormalities (endoscopy), continuous measurements that are pH dependent (pH monitoring) or not (Bilitec, impedance), and pathophysiology by measuring the relaxations of the LES (manometry). Recent evidence in adults reveals the clinical utility of Bilitec monitoring showing a possible role for duodenogastroesophageal reflux in a subset of patients who continue to report reflux symptoms in the setting of normalized esophageal acid exposure on high-dose proton pump inhibitor [9]. However, bile reflux can also be detected by impedance. Bilirubin is as toxic to the esophageal mucosa as acid, but the number of patients with esophagitis and only pathologic alkaline or nonacid reflux and normal acid reflux is small [79, 80].

In specific situations other techniques might be of interest such as lipid-laden macrophages, pepsin, and lactose in bronchial secretions. Abnormal pH monitoring does not accurately predict the risk for esophagitis [81, 82]. In a group of reflux patients with esophagitis, the sensitivity of pH metry is 88% and of scintigraphy is 36% [83]. In a group of patients with abnormal scintigraphy, the sensitivity of pH monitoring is 82%, endoscopy 64%, and manometry of the LES 33% [83]. Nonacid reflux may be inoffensive (simple postprandial) reflux at a neutral pH, but may also contain bile, which is toxic for the esophageal mucosa [84]. There is limited experience with esophageal bile monitoring in children.

The overall correlation between scintiscanning and pH monitoring is acceptable ($r = .78$) [85]. However, during simultaneous pH recording and scintiscanning, only 6 of 123 reflux episodes were recorded simultaneously [86]. There is no correlation between the number of reflux episodes detected using scintigraphy and pH monitoring [87]. Barium studies seem to have a much lower sensitivity to detect reflux episodes if pH monitoring is regarded as the gold standard [85]. According to many authors, there is a high frequency of both false-positive and false-negative results with barium studies that relates to the short investigation time on the one hand and the intensity of reflux-provoking maneuvers on the other hand. Fifteen-minute postprandial period color Doppler ultrasonography was compared with 24-h pH monitoring, showing agreement in 81.5 % [88]. However, if pH monitoring was considered the gold standard, the specificity of the color Doppler ultrasonography was as low as 11 %, and there was no correlation between the incidence of reflux episodes measured with both techniques [88]. A far higher number of reflux episodes is detected with impedance in comparison with pH monitoring because only 14.9 % of all reflux episodes are acid [89]. However, only 57 % of acid reflux episodes are detected with impedance [89].

Conclusion

The miniaturization of devices and electrodes has made pH monitoring a procedure that is easy to perform, even in the youngest children. Patient-related factors, such as feeding and physical activity, influence the results of pH monitoring. Impedance needs further evaluation in children before it can be recommended in clinical practice. Hardware- and software-related factors, as well as patient-related factors and recording conditions, determine the results of both pH and impedance recordings. In clinical practice, pH monitoring is of interest in a subset of patients in whom GERD is suspected but who present without clear regurgitation or emesis and to measure the efficacy of treatment such as acid suppression and/or prokinetics. Impedance has theoretical benefits over pH monitoring, but the technique still needs clinical validation.

Impedance is a costly and time-consuming technique, which allows for the detection of all reflux events. The diagnostic sensitivity of MII may correspond to that of the pH probe in untreated patients, but is superior to the pH probe in patients treated with antiacid medications [90]. Episodes detected only by pH monitoring are numerous in children; therefore, pH monitoring should be included in pH-MII analyses [91].

Day-to-day variability of the number of nonacid reflux episodes is considerable (1), and the detection of nonacid reflux episodes has a high interobserver variability (3). Although impedance clearly records more GER events than pH monitoring, the advantage and the relevance of recording more episodes of GER in daily clinical practice needs to be demonstrated. Thus, impedance still needs to be considered as a clinical research tool. The clinical relevance of the detection of weakly acid and nonacid reflux is also still a matter of research, because current data are inconclusive and specific treatment is not available. Symptom-correlation analysis, especially for extraesophageal symptoms, is likely to be more convincing with impedance than with pH monitoring.

Since pH monitoring is part of an impedance recording, it is likely that impedance will become more frequently performed in routine practice [92, 93]. From the data presented in the chapter, it emerges that it is currently difficult to draw conclusions on the precise advantages of the application of MII-pH in children to detect GER events. The heterogenicity of the studies (in terms of populations recruited and technical criteria such as time and symptoms association) and the lack of normative data and of outcome measures do not support this at present. More homogeneous inclusion criteria and analysis associated with a complete baseline and prospective clinical features are mandatory. Impedance is a new, promising technical development offering unexplored possibilities to investigate GER [92, 93]. Although many papers suggest a degree of usefulness, the technique is

still in a phase where the added value to other techniques in the routine workup of patients needs to be evaluated and demonstrated without scientific rigor.

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Assessment of GE Reflux: Esophageal Motility Studies

77

Samuel Nurko

Esophageal manometry is the gold standard for the diagnosis of primary motor disorders of the esophagus [1–3]. It is most frequently performed in children with dysphagia who have no evidence of anatomic obstruction, and the clinical use of esophageal manometry is in defining the contractile characteristics of the esophagus [1, 2]. Previous chapters review concepts on basic esophageal physiology and pathophysiology of esophageal dysfunction, as well as the technical aspects of performing esophageal motility studies. It is beyond the scope of the present chapter to discuss the pathophysiology of gastroesophageal reflux disease (GERD) in otherwise healthy children or children with malformations. Therefore, the present chapter will focus on reviewing the role that esophageal motility studies have in the evaluation and treatment of patients with suspected gastroesophageal reflux.

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Indications

Esophageal manometry has no role in the diagnosis of GER [1, 4] and is not indicated in the routine evaluation of patients with GER [1–3]. The exact role that the measurement of esophageal motility in the preoperative evaluation of children with GERD is not clear [1, 5]. The only clear role it has is when there is uncertainty about the correct diagnosis and a primary motility problem such as achalasia is suspected [6]. Esophageal manometry is also used to localize the LES before placement of a pH probe in patients with abnormal anatomy (e.g., hiatal hernia) [2] and may be useful in the evaluation of the intractable patient with severe esophagitis, as a low LES pressure of <10 mmHg has been associated with a poor response to medical therapy [7].

The use of esophageal manometry in patients with GERD before fundoplication has not been useful to predict postoperative outcome, so it does not need to be performed routinely before surgery (see below). There are no studies that have addressed the utility of esophageal manometry in the preoperative evaluation of children with diseases that may be associated with severe underlying motility disorders like scleroderma or esophageal atresia in which the surgery may create or aggravate a functional obstruction [1].

Even though esophageal manometry is not routinely indicated in the evaluation of patients with GER, it has been employed to try to better

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understand the pathophysiology of the disease, or as a way to predict which patients may benefit from anti-reflux surgery, or who may develop postoperative complications like dysphagia.

Esophageal Motor Abnormalities in Patients with GERD

As mentioned in previous chapters, it is thought that TLESRs (transient lower esophageal sphincter relaxations) are the main mechanism underlying reflux events [8] and that the number of TLSERs associated with acid reflux is significantly higher in those with GERD. Low or absent LES tone is a rare occurrence [4, 8], and most pediatric studies have failed to demonstrate a low LES tone in otherwise healthy patients with GERD with or without esophagitis [4, 9–12]. On the other hand, the prevalence of low LES pressure is much greater in patients with underlying congenital malformation like esophageal atresia [3, 13].

There is limited information regarding esophageal motor function in patients with GERD, particularly children. In adults with GERD, the most important motility abnormality in the esophageal body is referred to as "ineffective esophageal motility" (IEM). IEM is characterized by nontransmitted contractions and simultaneous contractions of reduced contraction amplitude (<30 mmHg) in the distal esophagus [4, 14, 15]. This ineffective esophageal motility has been associated with abnormal acid clearance [16]. In a recent study, Somani et al. [17] reported in adults a negative correlation between esophageal acid exposure and LES pressure, as well as between the amplitude of distal esophageal contractions and more severe esophagitis. These abnormalities are mainly found in adults with severe GERD and have been shown to impair esophageal clearance and contribute to the development of esophagitis [18]. Multiple studies in adults have documented that the subtle esophageal motility abnormalities that are found do not improve after successful therapy [19]. There is still an ongoing controversy as to whether impaired esophageal body motility in severe reflux disease is a primary disorder contributing to the pathogenesis of GERD or whether it is a consequence of long-standing reflux or esophageal inflammation [9, 20]. Therefore, it is unclear whether abnormal esophageal body contractions are the cause or consequence of peptic esophagitis. The information in children is limited. One study by Cucchiara et al. demonstrated nonspecific motor defects (simultaneous, broad-based, double-peak waves) in children with severe esophagitis and showed the dysfunction normalized with successful treatment [11]. Chitkara et al. in our laboratory showed there was no difference in the results of stationary manometry when comparing GERD patients with controls or by the degree of esophagitis [9]. Recently, Hoffman et al. [4] also showed that esophageal motor function in otherwise healthy children with GERD was normal. In a study using prolonged esophageal manometry, we also showed that even though baseline manometry was normal in all patients with GERD, there was a significant decrease in the total number of contractions per minute, before, during, and after a reflux episode, independently of the presence or not of esophagitis [9], suggesting the abnormalities may be secondary to an underlying motor disorder and not as a consequence of the inflammation.

On the other hand, children with underlying congenital malformations (like esophageal atresia) or severe systemic illness (like scleroderma) may have severe underlying esophageal dysmotility that predisposes them to severe GERD. Children with esophageal atresia have severely impaired dysmotility. This has been reported in up to 75–100 % of cases [21, 22]. The alterations described have been a low LES pressure and a lack of peristalsis, with esophageal contractions that tend to be simultaneous and weak although at times of normal amplitude especially in the lower esophagus [3, 13]. The peristaltic function of 22 adolescents and adults after esophageal atresia repair was also described with the use of ambulatory 24-h pH manometry [23]. All had diminished contractile activity, disorganized propulsive activity, and abnormal and ineffective peristalsis. This indicates a poor capacity for acid clearance and may explain the

frequent dysphagia and GER-related problems experienced by these patients. Given that not all patients with esophageal atresia develop GERD, manometry studies have been used to try to predict which are the patients at risk. In some studies, specific manometric abnormalities like a lack of distal esophageal contractions have been associated with the presence of GERD [24].

Esophageal abnormalities are present in one half to three quarters of patients with scleroderma, a much higher frequency than in patients with other collagen vascular disorders [25, 26]. The characteristic esophageal manometric findings are (1) incompetent lower esophageal sphincter, (2) low-amplitude esophageal contractions in the smooth portion of the esophagus, and (3) later alterations in the striated muscle section [25, 26]. The incompetent LES fails to provide an effective barrier against the gastric acid, and the abnormal peristalsis provides an inadequate acid clearance, predisposing the patients to severe complications from GER [25, 26]. By studying the relationship between the severity and extent of esophageal acid exposure and manometric abnormalities in patients with systemic sclerosis, it was concluded that the severity and extent of GER are closely related to the integrity of distal peristalsis. In a study of children with scleroderma, Flick and others [25] studied seven children with PSS and two with LS. The most frequent symptoms in patients with PSS were regurgitations, heartburn, and dysphagia. They showed that in 72 % of the patients with PSS (mean age 15; range 10–18), there was a decreased LES pressure, tertiary waves, or feeble contractions. They found a strong correlation between the presence of Raynaud's phenomenon and esophageal symptoms but no correlation with disease duration. There was a correlation between dysphagia and the presence of esophageal motor abnormalities.

Therefore, from all these observations, it can be concluded that the presence of severe esophageal dysmotility, mostly abnormal LES pressure and abnormal distal esophageal contractions, predisposes patients to have more severe GERD. In reality, we are dealing with two distinct populations: the otherwise healthy patient in which there may be some nonspecific motility disorders that may or may not improve after successful therapy, but on the other, patients with severe underlying esophageal motor disorders, in which the primary motor problem predisposes them to severe GERD and its complications and in which surgery may create a functional obstruction.

Role of Esophageal Manometry in the Preoperative Evaluation of Patients with Intractable GERD

The controversy if the esophageal motor abnormalities in GERD are primary or secondary to inflammation in otherwise healthy patients is not only academic but has practical consequences as dysphagia is one of the main complications after fundoplication, and it has been suggested that underlying motility abnormalities of the esophagus may be responsible. Therefore, trying to better understand the genesis of postoperative dysphagia is one of the main indications that have been used in the past for the performance of esophageal motility in patients with GERD.

In general, once a decision to perform a fundoplication has been made, esophageal manometry has not been shown to predict clinical outcome [6]. The role that preoperative esophageal peristalsis plays in the development of dysphagia after fundoplication has been controversial [27]. The dysphagia may be related to either a wrap that is too tight around an esophagus with good peristaltic function or secondary to a functional obstruction created by the inability of some damaged esophagus to produce enough force to propel the food into the stomach.

The role that preoperative esophageal peristalsis plays in the development of dysphagia has been controversial [27, 28]. It was initially suggested that care should be exercised when a fundoplication is performed in patients with abnormal esophageal peristalsis [27, 28]. Since then, the relationship between preoperative esophageal motor abnormalities and postoperative dysphagia has been questioned [27, 29, 30]. In a study after laparoscopic Nissen in 81 adults

that had baseline esophageal motility, there showed no difference in the prevalence of dysphagia up to a year after the operation (12.5 % vs. 15 %), when comparing the 48 patients with normal motility, with the 33 with abnormal esophageal function [27]. They suggested that there was poor correlation between the preoperative manometry and outcome and that abnormal esophageal peristalsis is not a contraindication to perform the operation [27]. Another recent prospective randomized clinical trial of 200 patients randomized either to Nissen (360°) or Toupet fundoplication (270°) studied esophageal motility before and after the surgery. They found that preoperative esophageal dysmotility reflected more severe disease, but it did not affect postoperative clinical outcome. In 85 %, the motility remained unchanged, as it was not corrected by the fundoplication (independent of the surgical procedure performed). In 20, it improved, while in 9 it worsened. They concluded that preoperative esophageal dysmotility requires no tailoring of the surgical management [30]. A recent study showed no difference in postoperative dysphagia after a Nissen laparoscopic fundoplication when they compared 28 patients that met manometric criteria for abnormal esophageal motility (<30 mmHg mean contractile pressure or <80 % peristalsis) and 63 patients with normal esophageal function, indicating that the presence of esophageal motor abnormalities does not seem to increase the risk for postoperative problems [31] and does not need the performance of a partial fundoplication. There are also some recent studies that in fact suggest that fundoplication improves ineffective peristalsis in patients with GERD [31]. These studies have not included patients with severe underlying conditions like scleroderma or other severe motility disorders.

No similar studies to determine the incidence of dysphagia after fundoplication taking in account preoperative manometric findings have been performed in children, but current information suggests there is no need to routinely perform an esophageal manometry before surgery in otherwise healthy children [2, 3], given that most patients have normal esophageal motility.

The considerations in those patients with conditions that are associated with underlying severe motility abnormalities are different, as those are the patients that may have worse outcomes after surgery. A preoperative manometry may be useful in those children with scleroderma or esophageal atresia, as a fundoplication may cause a functional obstruction because of the lack of peristalsis [25, 32]. Patients with scleroderma provide a model in which there is underlying primary severe esophageal dysmotility that leads to intractable GERD that often requires surgical intervention. Most studies in scleroderma patients document postoperative dysphagia in between 31 and 71 % after fundoplication [25, 26, 33], but there are no prospective studies that have tried to correlate the preoperative manometric findings with outcome. There are some studies that have shown that the absence of distal esophageal peristalsis in patients with esophageal atresia may be correlated to the presence of severe GERD and that in those circumstances modified fundoplications may be needed to avoid the creation of a functional obstruction [24, 32]. However, there are no prospective studies that have shown that the performance of a manometry indeed changes the surgical management or the outcome in those patients.

Another indication for esophageal manometry in GERD patients is in the evaluation of those with a failed fundoplication, as it is very important to be sure there is no underlying primary disorder before a new surgery is performed. Low et al. [34] reported in a series of patients that underwent secondary operations for failed Nissen procedures that six patients presenting with severe postoperative dysphagia had evidence of primary esophageal motility disorders (four collagen vascular diseases and two with achalasia) that were not diagnosed before surgery, indicating the importance of assessing esophageal motility before the initial operation or reoperation if a primary motility disorder is suspected [28].

Advances in Esophageal Manometry and Their Potential Use in the Evaluation of Patients with GERD

It has been suggested that one of the main reasons that the use of esophageal manometry in the preoperative evaluation of patients with GERD

has not been found to be useful is that it may not accurately reflect true esophageal transit. In fact, the advent of multichannel intraluminal impedance combined with manometry has allowed the simultaneous evaluation of esophageal contractions and bolus transit (Fig. 77.1) [1, 35–37]. The technique has been validated with the simultaneous use of manometry, videoesophagram, and impedance, and the authors concluded that impedance monitoring is a valid transit test [35]. During the test, either liquid swallows (usually saline) or viscous swallows are studied, and the transit through the esophagus is measured by analyzing the changes in impedance. It has been shown that for both liquid and viscous boluses, the likelihood of impaired bolus clearance is related to the number of segments with hypotensive pressure waves [38]. Because the transit of viscous material may be more sensitive than liquid boluses in assessing mild transit abnormalities, both bolus types have been used. Different studies have shown that normal bolus transit in healthy individuals occurs at least in 80 % of liquid and 70 % of viscous swallows when solid-state catheters are used [39] or in 70 % of liquid and 60 % of viscous, when perfused catheters are utilized [40]. No similar information is available for healthy children, but preliminary information in children has shown that the technique is feasible [1, 41]. Studies in adults have shown that the manometric evidence of ineffective peristalsis may underestimate the true bolus clearance and that the combined impedance with manometry may be a more sensitive technique to assess esophageal function and to evaluate patients with dysphagia [38, 39]. The combined use of manometry and impedance has shown that approximately 97 % of normal peristaltic swallows have normal bolus transit but also that almost half of manometrically ineffective peristalsis had normal liquid transit [39]. In children, preliminary information has shown that effective bolus clearance by impedance is present in 75 % of swallows that had ineffective peristalsis [41]. In a report of 350 patients, it was found that all patients with achalasia and scleroderma had abnormal bolus transit time but that 51 % of those with ineffective esophageal motility and 55 % of those with diffuse esophageal spasm had normal bolus transit. Furthermore, almost all with normal esophageal manometry, nutcracker esophagus, poorly relaxing LES, hypertensive LES, and hypotensive LES had normal bolus transit [37]. This indicates that the addition of impedance and the study of bolus transit may provide a more accurate diagnosis of esophageal dysfunction as compared to esophageal manometry alone [37]. Recent studies demonstrate that combined impedance manometry provides important additional information about esophageal motility as compared to conventional manometry: (1) monitoring of bolus transport patterns, (2) calculation of bolus transit parameters, (3) evaluation of bolus clearance, (4) monitoring of swallow-associated events such as air movement and reflux, and (5) investigation of the relationships between bolus transit and LES relaxation [42]. It can therefore be concluded that combined esophageal manometry with impedance is a new technique that allows the simultaneous study of both manometry and transit and therefore provides a validated tool to study esophageal transit and its relation to motility patterns without radiation exposure [35, 36]. Future studies will demonstrate if the addition of the impedance to the manometry will prove to be more sensitive to detect which are the patients that will develop dysphagia after fundoplication.

Another advance in the study of esophageal physiology has been the use of high-resolution manometry (HRM) (Fig. 77.2) [1, 43]. The basic concept being that by vastly increasing the number of recording sites and decreasing the spacing between them, one can completely define the intraluminal pressure environment without spatial gaps between recording sites and, consequently, with minimal movement-related artifacts [43, 44]. The vastly increased quantity of data associated with HRM studies creates new challenges with respect to data display and data analysis. Hence, algorithms have been devised to smoothly interpolate HRM data, making it appear as a space-time continuum that can be displayed as isobaric contour plots. The advantages of isobaric contour plots are multiple, but the most evident is that it provides a seamless, dynamic representation of peristalsis at every axial position within and across the esophagus

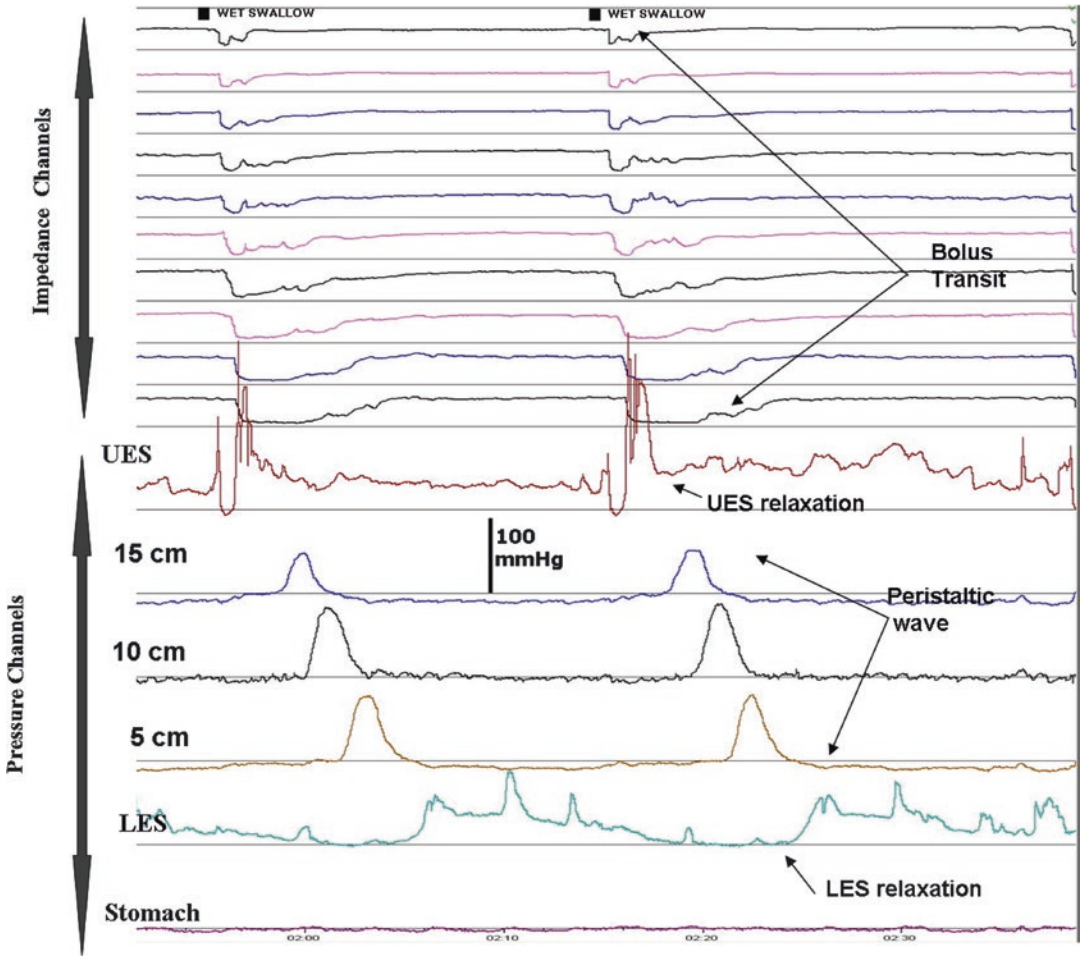

Fig. 77.1 Normal esophageal manometry. This represents a combined manometry and impedance study. The upper ten channels represent impedance measurements, while the lower six channels represent pressure measurements. A normal response to wet swallows can be observed. There are UES and LES relaxations, followed by normal esophageal peristalsis. The impedance channels show a normal progression of a saline bolus. *UES* upper esophageal sphincter, *LES* lower esophageal sphincter (Adapted with permission from Rodriguez and Nurko [1])

[43, 44]. Recent studies have shown that HRM predicts the presence of abnormal bolus transport more accurately than conventional manometry and identified clinically important motor dysfunction not detected by manometry and radiography [45–47]. It has been suggested that HRM predicts bolus movement more accurately than conventional manometry [47]. The recent addition of impedance to the HRM will also provide further insight into esophageal function [1] (Fig. 77.2). The use of HRM has recently been shown to better characterize peristaltic dysfunction in patients with GERD, particularly those with erosive esophagitis [16]. They showed that the esophageal motor response after solid swallows was even more impaired, suggesting that now it is possible to perform studies with swallowed material that increases the workload of the esophagus; HRM may become a more sensitive tool in the evaluation of patients with GERD [16]. The exact role that HRM, or HRM with impedance, will play in the evaluation of preoperative patients before reflux surgery still needs to be defined, and there is still no available information about its use for this purpose in children either.

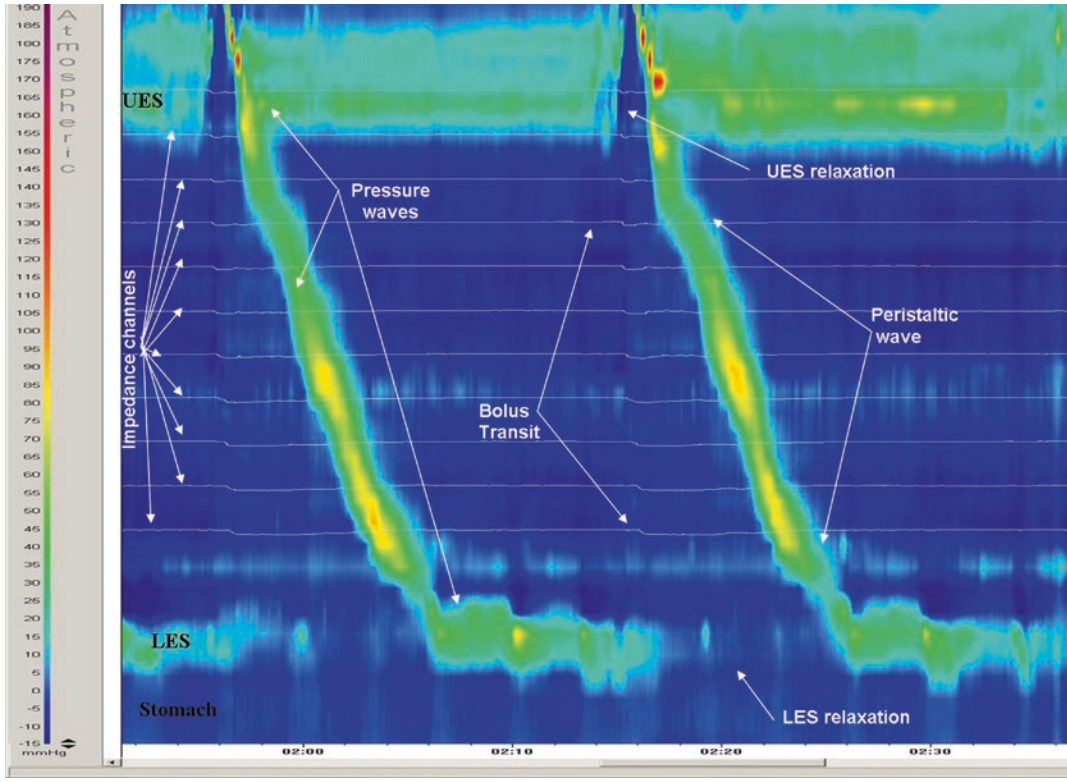

Fig. 77.2 Normal high-resolution manometry. Contour plot obtained with the use of high-resolution manometry and impedance in a healthy child. The colors represent different pressure intensity, as can be seen in the scale. A normal response to wet swallows can be observed. There are UES and LES relaxations, followed by normal esophageal peristalsis. The impedance channels in white show a normal progression of a saline bolus (bolus transit) (Adapted with permission from Rodriguez and Nurko [1])

Conclusions

At present, there is no evidence to show the benefit for the routine preoperative assessment of peristaltic function in otherwise normal children with GERD that will undergo fundoplication. However, esophageal manometry may have a role when there is severe preoperative dysphagia or atypical symptoms or when severe underlying dysmotility is known to occur. In children, the latter problem is commonly found in patients with scleroderma or esophageal atresia [32, 48], in which a fundoplication may create a functional obstruction in a dysmotile esophagus. New advances in esophageal motility testing may give new insight into those GERD patients that may develop complications after surgery.

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Esophageal Intraluminal Impedance

78

Tobias G. Wenzl

Electrical impedance is defined as the relation of voltage (U) to current (I). It is measured in Ohm (Ω) and is, similar to resistance, inversely proportional to electrical conductivity. The multiple intraluminal impedance (MII) technology is based on the measurement of impedance in an organ lumen and the change of impedance during the passage of a bolus through this lumen. To measure impedance, cylindrical electrodes are placed on a hollow catheter. For signal transduction and registration, these electrodes are connected via thin wires inside the catheter with impedance-voltage converters and a display/recording unit outside the body. Impedance is measured bipolarly between two electrodes on a catheter. These two electrodes form an impedance channel, representing a defined area of the luminal organ. The total length of all channels is defined by the number of and distance between the electrodes [6].

Impedance changes characteristically depend on the content of the bolus. The electrical conductivity of air is close to zero, whereas the electrical conductivity of a liquid bolus is high, even compared to the conductivity of the muscular organ wall. All components (air, bolus, organ wall, body) together form a volume conductor around the catheter and the impedance electrodes (Fig. 78.1).

By high-frequency registration (50–100 Hz registration rate) in the esophagus, it is possible to distinguish between the resting phase, the bolus passage, and the muscular contraction in every single impedance channel. During the resting phase, due to the close proximity of the relaxed muscles (low conductivity) to the measurement electrodes, the impedance baseline is recorded. The increase of impedance just before the bolus passage, e.g., during a swallow, represents air that is propelled in front of the bolus. This is followed by a decrease of impedance after entry of the bolus into the measuring segment. The consecutive increase of impedance represents bolus exit and the contracted muscle wall after bolus passage through the measuring segment. Finally, muscles relax and impedance values return to baseline [3].

By placing multiple impedance channels consecutively on a single catheter inside a luminal organ, e.g., the esophagus, it is possible to determine the direction, height, and velocity of the bolus movement [6].

All impedance channels are recorded digitally and displayed simultaneously. Stationary or portable recording systems are available. Impedance measurements are analyzed using dedicated software and manually-visually to detect the typical changes during the passage of a bolus. If these changes appear in the most proximal impedance channels first and then in

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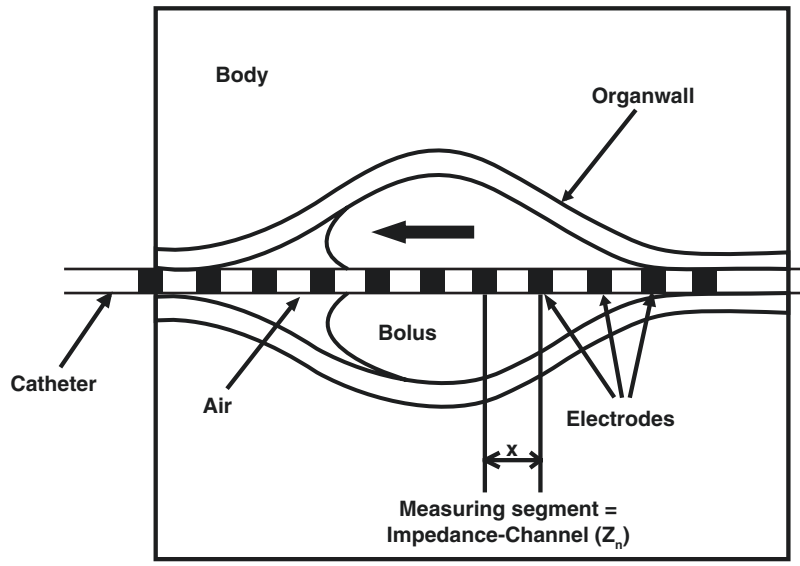

Fig. 78.1 Multiple intraluminal (electric) impedance procedure. Cross section through a luminal organ inside the body, organ wall, intraluminal impedance catheter, air, and bolus. *Arrow*: direction of bolus movement. Impedance (Z) is measured bipolarly between adjacent electrodes (= impedance channel, Z_n). Defined electrode distance (x) and number of channels (n)

the more distal impedance channels, this is interpreted as antegrade bolus movement, e.g., a swallow. If these changes appear in the most distal impedance channels first and then in the more proximal impedance channels, this is interpreted as retrograde bolus movement, e.g., a gastroesophageal reflux (GER) (Fig. 78.2). As the software allows the use of different time scales on the screen, longer episodes can be displayed completely, but also a more detailed analysis can be performed using a magnified view.

In a pilot study, the conductivity and impedance of various tissues, liquids, and foodstuff were measured in vitro using an eight-channel impedance catheter. A measuring current of <6 μA was used, as this is well below the stimulation threshold of human nerves and muscles and therefore does not interfere with the impedance registration of gastrointestinal motility. The theoretical principle of the technology was confirmed with these experiments, and the typical phases of a bolus passage were verified [6].

In vivo studies in the esophagus and duodenum of healthy volunteers confirmed the bolus phases found in vitro and the general potential of the method. Typical impedance patterns during swallows and muscular contractions were recorded and analyzed [3].

In studies on healthy adults, fluoroscopy, manometry, and MII of the esophagus were performed simultaneously. These studies delivered information regarding normal motility during the antegrade passage (swallow) of solid meals and liquids. The potential of recording GER and its clearance was demonstrated, the temporal relation of pressure changes in the esophagus, and the different impedance phases were analyzed (Fig. 78.3). The passage of air and a bolus results in relevant changes of impedance, but only little pressure increase. Maximum pressure is only experienced when the bolus exits the measuring segment.

From the defined electrode distance and the time difference between appearances of the typical impedance pattern in the neighboring impedance channels, the bolus velocity and length could be calculated for every organ segment. With this technology, it is possible to analyze changes of bolus velocity and length during the passage through the esophagus. A difference between the bolus velocity and the contraction wave velocity became apparent.

In a first clinical trial, adults with reflux esophagitis and healthy controls were examined with MII and manometry. MII patterns of the upper and lower esophagus were compared after test meals. A significant reduction of bolus velocity in

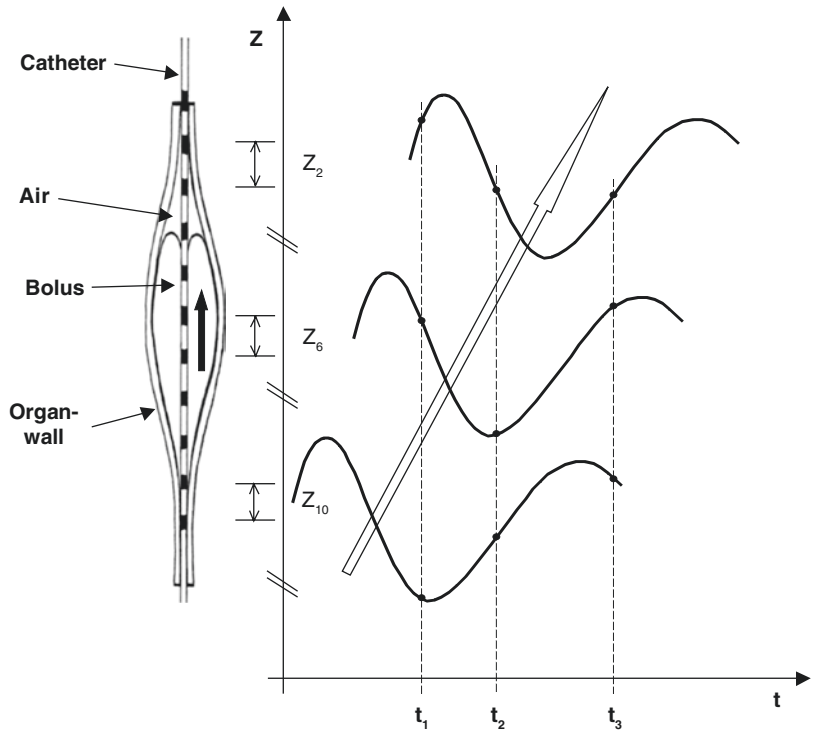

Fig. 78.2 Typical impedance changes during bolus passage through multiple measuring segments. Cross section through a luminal organ. *Thick arrow*: direction of bolus movement. Impedance (Z) over time (t). Impedance values of channel 2 (Z_2), 6 (Z_6), and 10 (Z_{10}) at the time of bolus passage. Typical sequential impedance changes (*thin arrow*) during bolus passage, first appearing in Z_{10}, then in Z_6, and ultimately in Z_2. t_1: bolus passage through Z_{10}, bolus entry in Z_6, and air entry in Z_2. t_2: bolus exit from Z_{10}, bolus passage through Z_6, and bolus entry in Z_2. t_3: return to baseline in Z_{10}, contracted muscular wall in Z_6, and bolus exit from Z_2

the aboral direction was recorded in all study individuals. Velocity was hereby inversely proportional to the viscosity of the test meal. Patients with reflux esophagitis showed a significant delay of bolus passage in the distal esophagus as compared to healthy controls; impedance values stayed well above baseline and only slowly returned to baseline after the second swallow. As no corresponding changes were documented with manometry, these were most likely non-occluding contractions.

In the next trials, MII was combined with pH-metry to study adults with reflux esophagitis. Impedance data was analyzed for the typical pattern of retrograde bolus movement; additionally, the pH of the GER episode could be defined. Shortly after the development of impedance and pH registration on a single catheter, the technology was applied in infants [7]. Impedance channels covered the lumen from the hypopharynx to the most distal esophagus [11].

The most proximal impedance channel displaying a drop of impedance resembling bolus presence was defined as height reached by the reflux. Most GER in infants reached the most proximal channel and occurred early postprandially.

The beginning of a bolus reflux was defined as a drop of impedance of at least 50 % of the impedance baseline prior to the reflux episode. It was shown that even very small bolus volumes were detectable by intraluminal impedance [4].

Volume clearance was defined as the time interval from bolus entry until bolus exit, i.e., the return of impedance values to at least 50 % of the impedance baseline prior to the GER. This was derived from in vitro studies and known to correspond to a clearance of more than 90 % of the bolus from the measuring segment [6]. Acid

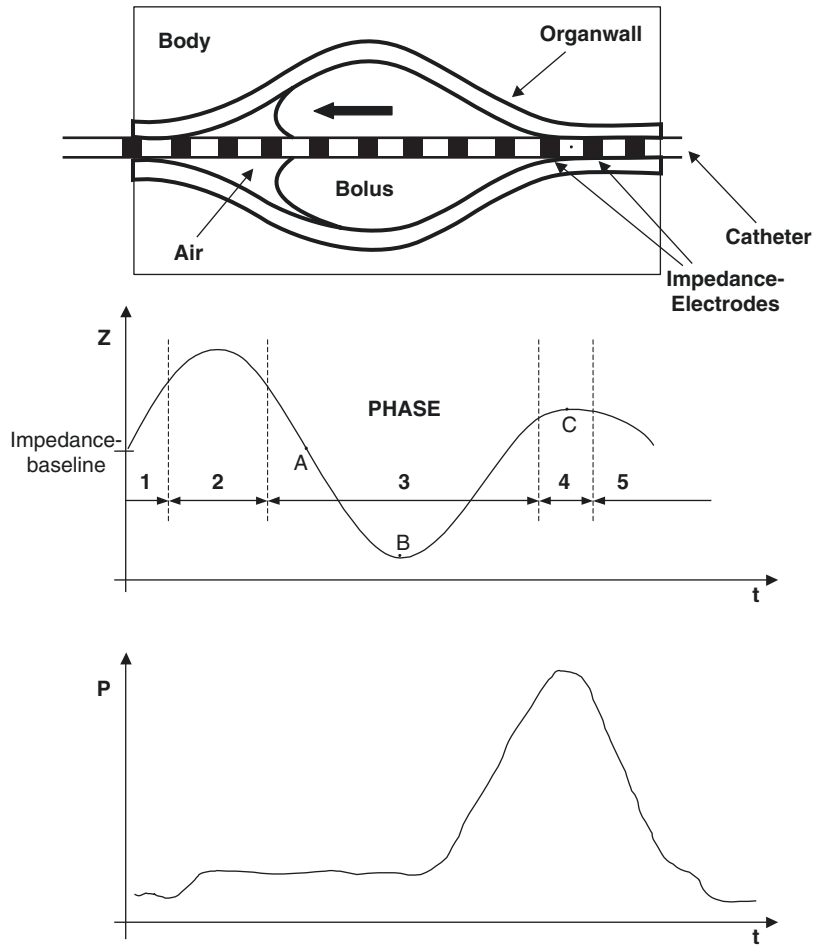

Fig. 78.3 Typical impedance and pressure changes during bolus passage through a measuring segment. Cross section through a luminal organ. *Arrow*: direction of bolus movement. Impedance (*Z*) and pressure (*P*) over time (*t*). Increase of impedance and slight increase of pressure in phase 2. Maximum pressure increase (phase 4) during segmental muscular contraction. (*A*) Entry of bolus head and return of impedance to baseline; (*B*) maximum bolus conductivity and lowest impedance; (*C*) maximum luminal occlusion

clearance was defined as the time interval from the drop of pH below threshold (usually pH 4) until its return to values above pH 4. Due to the chemical definitions, GER with pH <4 was defined as being acid GER, with pH 4–7 as weakly acidic GER, and with pH >7 as being nonacid or alkaline GER. In almost all GER, volume clearance was shorter than acid clearance and achieved after a single swallow.

All studies in infants clearly demonstrated that the major amount of GER episodes were weakly acidic, with pH monitoring alone showing a very low sensitivity for GER detection in all pH ranges.

This was found to be the new definition of gastroesophageal reflux in children [1, 5]. Color-coding of impedance changes improved visual analysis of the tracings significantly (Fig. 78.4). To date, multiple combined impedance-pH measurements have been performed in clinical routine in children of all age groups worldwide [9, 10]. International standards have been created for the procedure. The establishment of normal values and the validation of the automated analysis software in pediatric patients are in the focus of current collaborative efforts. The most recently published international

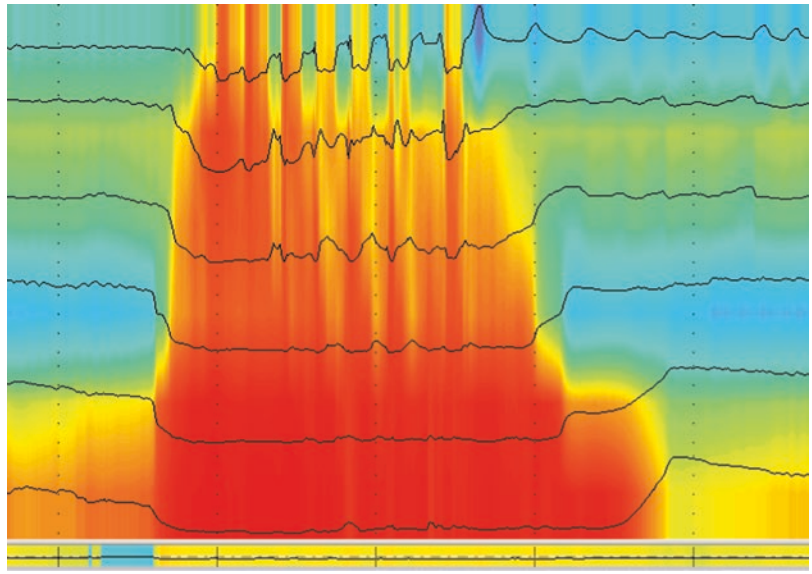

Fig. 78.4 Typical impedance tracing of a gastroesophageal reflux. Impedance channels color-coded regarding absolute impedance value (*blue* high impedance; *red* low impedance)

guideline on gastroesophageal reflux in children describes combined multiple esophageal impedance-pH recording as being superior to pH monitoring alone for evaluation of GER-related symptom association [2, 8].

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Endoscopy with Biopsy for Esophagitis

79

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Endoscopy of the whole upper GI tract (esophagus, stomach, and duodenum) with multiple biopsies is the investigation of choice in the evaluation of infants and children with symptoms suggestive of esophagitis [1, 2]. From the technical and technique aspects, useful texts to refer to are available for pediatric-specific endoscopy nowadays [3, 4]. Endoscopy should be performed only by experienced and qualified pediatric endoscopists trained in endoscopy in infants and children, with appropriate back up from pediatric anesthesiologists, and most importantly pediatric GI histopathologists. Technology now allows us to perform esophagogastroduodenoscopy (EGD) in even the smallest infants using 5.5 mm diameter instruments [5, 6]. EGD and biopsy, however, are useful only if it will lead to alteration in diagnosis, treatment, or prognosis, and useful position papers for the individual and conjoint North American and European Pediatric Gastroenterology Societies have been published on reflux and esophagitis, including the place of endoscopy in management of these conditions [2, 7–11]. Short general anesthetic is preferable to IV sedation for the procedure for reasons of safety, ease, and success of a complete and comprehensive study [12], although, with an anesthesiologist present, short-acting agents such as propofol can be used.

Macroscopic appearances of the esophagus revealing, for instance, erythema, erosions, or ulceration will guide biopsy acquisition from the areas and lesions most likely to yield highest diagnostic return. A normal endoscopy or an absence of macroscopic lesions does not exclude the presence of histologic esophagitis [13], and with our increased understanding of the variety of etiologies for esophagitis, biopsies have an enhanced role in altering management. The counterargument to this was previously advanced to defend endoscopy without esophageal biopsy in cases in which no macroscopic lesions existed [1, 14, 15], and these authors also suggested that the increase in the cost of endoscopy, when combined with biopsy, may mitigate against the latter in some countries. This is generally held to be an outdated philosophy. No conjecture exists when performing biopsies for detection or surveillance of Barrett's esophagus in which four-quadrant biopsies between 1 and 5 cm from the GEJ can be most helpful – the so-called Seattle protocol, using jumbo biopsy forceps [16].

Recent global consensus guidelines define reflux esophagitis as the presence of endoscopically visible breaks in the esophageal mucosa at or immediately above the GE junction [17–19]. Evidence from adult studies indicates that visible breaks in the esophageal mucosa are the endoscopic sign of greatest interobserver reliability

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[20–22]. Operator experience is an important component of interobserver reliability [23, 24]. Mucosal erythema and an irregular Z-line are not reliable signs of reflux esophagitis [21, 22]. Grading the severity of esophagitis, using a recognized endoscopic classification system is useful for evaluation of the severity of esophagitis and response to treatment. The Hetzel-Dent classification [20] has been used in several pediatric studies [11, 25, 26], while the Los Angeles classification [19] is generally used for adults but is suitable also for children. The presence of endoscopically normal esophageal mucosa does not exclude a diagnosis of nonerosive reflux disease or esophagitis of other etiologies [27–29].

Classifications and scoring systems are employed in an attempt to semi-quantify the appearances suggestive of esophagitis, which helps to remove interobserver error. The most widely used of these are the modified Savary-Miller criteria (Table 79.1) [20]. The classification of Hetzel and colleagues has also been employed (Table 79.2). However, a criticism of the latter is that distinction between grades 0 and 1 is relatively subjective [11]. These classification systems have uses other than introducing objectivity, namely, that the pretreatment grade of esophagitis is of value in predicting the pattern and severity of acid reflux and healing rates [30], and improvement to grade 0 or 1 would be the usual aim, in either classification, of treatment.

Table 79.1 Proposed endoscopic classification of esophagitis

Grade	Features
Normal mucosa	
1	Nonconfluent erosions appearing as red patches or striae just above the Z line[a]
	Erythema or loss of vascular pattern
2	Longitudinal noncircumferent erosions with a hemorrhagic tendency of the mucosa
2a	1 plus bleeding to light touch (friability)
2b	1 plus spontaneous bleeding
3	Circumferent tendency; no strictures
4a	Ulcerations with stricture or metaplasia
4b	Stricture without erosions or ulcerations

Adapted from Savary and Miller
[a]Z line defined as junction between columnar gastric fungal mucosa and stratified esophageal mucosa

The specific macroscopic appearances of conditions other than GER esophagitis are noted in the relevant sections on pathogenesis above. Hassell suggests that erosions usually found on the tops of esophageal folds are specific for reflux disease, often with a rim of erythema around the white erosions [14]. However, these may mimic, for instance, Crohn's disease. Gupta and colleagues suggest that vertical lines in the distal esophageal mucosa are a true endoscopic manifestation of reflux esophagitis in children (Fig. 79.1) [31]. In severe ulcerated esophagitis, objective proof of recovery following treatment is important, and repeat endoscopy between 3 and 12 weeks later is generally recommended.

Table 79.2 Endoscopic classification of esophagitis

Grade	Features
No mucosal abnormalities	
1	Erythema, hyperemia, mucosal friability
2	Superficial erosions affecting <10 % of the distal 5 cm of esophageal squamous mucosa
3	Superficial erosions or ulceration of 10–50 % of the mucosal surface of the distal 5 cm of esophageal squamous mucosa
4	Deep peptic ulceration anywhere in the esophagus or confluent erosion of >50 % of the mucosal surface of the distal 5 cm of the esophageal squamous mucosa

Adapted from Hetzel et al.

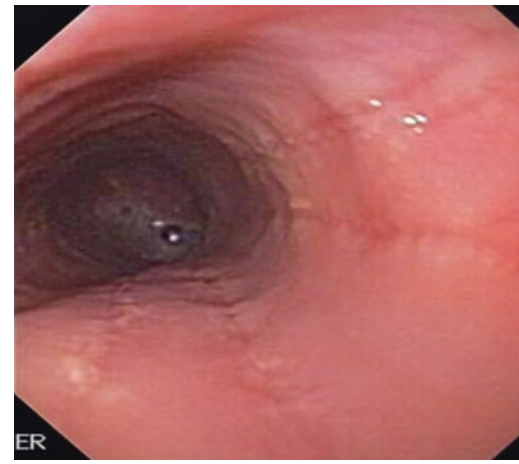

Fig. 79.1 Eosinophilic esophagitis: not the longitudinal furrowing and the white papules with a degree of circular indentations known as 'trachealisation' of the esophagus

Generally, it is held that although the majority of esophagitis is due to reflux, the esophageal appearances themselves do not reliably differentiate between reflux and other causative pathologies. This is perfectly demonstrated in the diagnosis and management of esophagitis in children with cancer, in whom esophagitis is a common occurrence but whose etiology is not predicted accurately by clinical observations (e.g., oral candidiasis does not predict for candidal esophagitis) or by macroscopic endoscopic appearances [32] – hence, the requirement for confirmatory biopsy and histology.

EE and GERD have very similar symptoms and signs and can be best distinguished by endoscopy with biopsy. A key difference endoscopically is that EE is not generally an erosive disease, but has its own typical endoscopic features such as speckled exudates, trachealization of the esophagus, or linear furrowing. In up to 30 % of cases, however, the esophageal mucosal appearance is normal [27]. When eosinophilic esophagitis is considered as part of the differential diagnosis, it is advisable to take esophageal biopsies from the proximal and distal esophagus [27]. Mucosal eosinophilia may be present in the esophageal mucosa in asymptomatic infants <1 year of age [33], and in symptomatic infants, eosinophilic infiltrate may be due to milk protein allergy [34].

There is insufficient evidence to support the use of histology to diagnose or exclude GERD. The primary role for esophageal histology is to rule out other conditions in the differential diagnosis, such as eosinophilic esophagitis, Crohn's disease, Barrett's esophagus, infections, and others. This conclusion concurs with that of a global pediatric consensus group [17]. When symptoms suggestive of GERD are present in adolescents or adults in the absence of erosive esophagitis, the clinical entity is known as nonerosive reflux disease (NERD). In NERD, there is no evidence that esophageal histology makes a difference to clinical care decisions, i.e., patient treatment is guided by symptoms, whether or not reactive histologic changes are present on biopsy.

At endoscopy, accurate documentation of esophagogastric landmarks is necessary for the diagnosis of hiatal hernia and endoscopically suspected esophageal metaplasia (ESEM) [35–40]. This is of particular importance in children with severe esophagitis, in whom landmarks may be obscured by bleeding or exudate, or when landmarks are displaced by anatomic abnormalities or hiatal hernia [35, 36, 41]. In these circumstances, a course of high-dose PPI for at least 12 weeks is advised, followed by a repeat endoscopy, in order to remove the exudative camouflage and better visualize landmarks [36, 42].

Histology

A diagrammatic representation of an esophageal cross-section is shown in Fig. 79.2. Nowadays, biopsies are endoscopic, but suction biopsies have been assayed in the past and probably yield

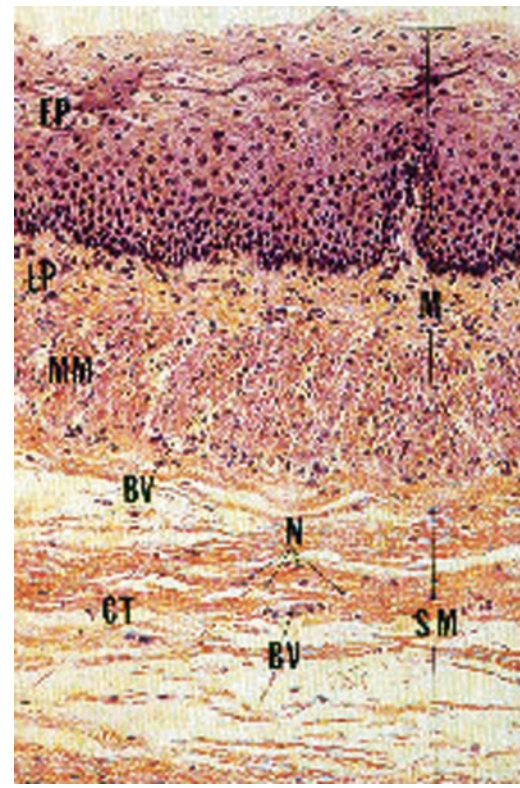

Fig. 79.2 Histological cross-section of the esophagus. *SM*: smooth muscle; *MM*: muscularis mucosa; *EP*: epithelium; *M*: mucosa; *LP*: lamina propria; *N*: nerve; *BV*: blood vessel; *CT*: connective tissue

Table 79.3 Grading criteria for histologic appearance of esophagus

Grade	Histologic criteria	Clinical diagnosis
0	Normal	Normal
1a	Basal zone hyperplasia	Reflux
1b	Elongated stromal papillae	Reflux
1c	Vascular ingrowth	Reflux
2	Polymorphs in the epithelium ± lamina propria	Esophagitis
3	Polymorphs with epithelial defect	Esophagitis
4	Ulceration	Esophagitis
5	Aberrant columnar epithelium	Esophagitis

Adapted from Knuff et al. and Leape

a deeper, more satisfactory biopsy [43]. When suction biopsies were added to conventional grasp biopsy technique in a study by Hyams and colleagues, the histologic diagnosis of esophagitis was increased from 60 % to 83 % of cases, although if one takes more biopsies, one would expect a greater diagnostic yield given the patchy nature of childhood esophagitis; hence, this cannot be used to suggest that suction biopsies are superior in pediatric practice [44]. Friesen and colleagues showed no statistically significant difference in predictive value for esophagitis in infants between the two techniques [29]. Correctly oriented endoscopic biopsies (e.g., immediate orientation on filter paper or nylon mesh in 10 % formalin) are, however, perfectly adequate, and so-called "crocodile" biopsy forceps, which allow the operator to biopsy perpendicular to the esophageal lumen, may be preferable. Large-cup ("jumbo") biopsy forceps are increasingly used and are mandatory for the surveillance of Barrett's esophagus using the so-called Seattle protocol (quadrantic biopsies every 1 cm above the GEJ involving the distal 5 cm of the esophagus) because they yield deeper biopsies [16]. The site of biopsy should be above the distal 15 % of the esophagus to avoid confusion with normal variance [44]. Biopsies should include epithelium, lamina propria, and muscularis mucosae and be oriented in a perpendicular plane to maximize diagnostic yield, such as evaluating properly the thickness of the basal zone, vascular ingrowth, and the elongation of the stromal papillae. For definitive diagnosis, the presence of two of three of these features is preferable, which will not be possible with poorly oriented

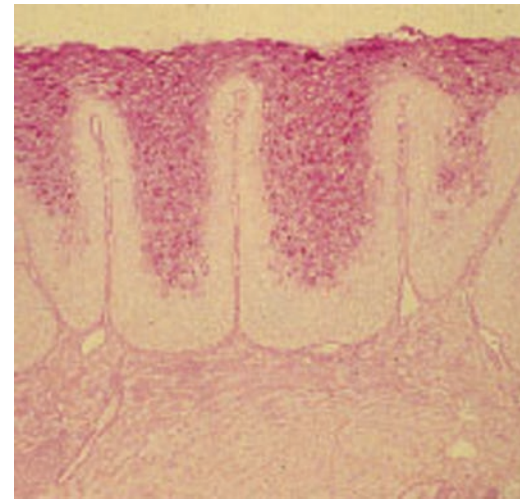

Fig. 79.3 GOR changes with papillary height change and the papillary to epithelium ratio approximately 90 % where normal is <33 % approx

tissue [1, 2]. Vertical macroscopic lines may be useful in determining histological esophagitis [26]. The classic histologic findings of GER esophagitis are displayed in Table 79.3 (Fig. 79.3). Elongation of stromal papillae is a useful indicator of reflux, and basal zone hyperplasia is defined when the papillae are more than 25 % of the entire thickness of the epithelium, and if more than 50 %, then the papillae are considered to be elongated [45].

The diagnostic yield of endoscopy is generally greater if multiple samples of good size and orientation are obtained from biopsy sites that are identified relative to major esophageal landmarks [35, 36, 41]. Several variables have an impact on the validity of histology as a diagnostic tool for reflux esophagitis [29, 46]. These

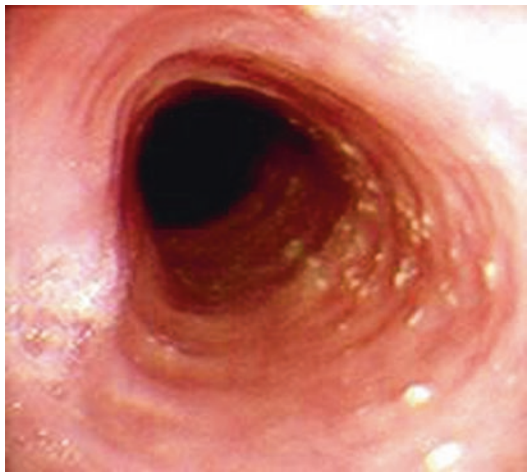

Fig. 79.4 Features of eosinophilic esophagitis although the white plaques may be mistaken for esophageal candida

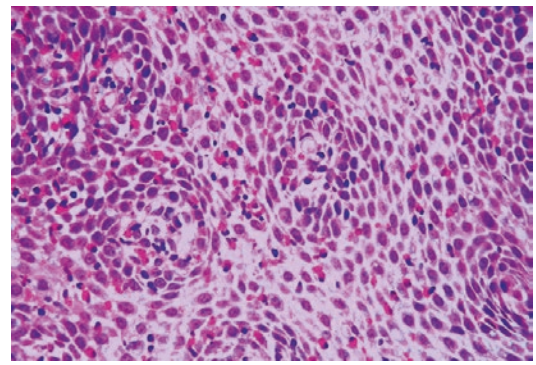

Fig. 79.5 Eosinophilic infiltration of the esophagus in eosinophilic esophagitis

include sampling error due to the patchy distribution of inflammatory changes and a lack in standardization of biopsy location, tissue processing, and interpretation of morphometric parameters. Histology may be normal or abnormal in nonerosive reflux disease (NERD) because GERD is an inherently patchy disease [29, 47]. Histologic findings of eosinophilia, elongation of papillae (rete pegs), basal hyperplasia, and dilated intercellular spaces (spongiosis) are neither sensitive nor specific for reflux esophagitis. They are nonspecific reactive changes that may be found in esophagitis of other causes, or in healthy volunteers [28, 29, 46, 48–54]. Recent studies have shown considerable overlap between the histology of reflux esophagitis and eosinophilic esophagitis [27, 28, 34, 55]. Many histologic parameters are influenced by drugs used to treat esophagitis or other disorders.

Esophageal mucosal eosinophilia has been described in both suspected cow's milk-associated reflux esophagitis [15, 56] and reflux esophagitis [57], as well as in other conditions, such as eosinophilic esophagitis (Figs. 79.4 and 79.5) [58]. The clinical significance of eosinophils and their role in the pathogenesis of mucosal injury are poorly understood and are the subject of recent debate [14, 15, 59]. Some have suggested an active role for eosinophils in the inflammatory process of esophagitis and have supported this with the observation of resolution of symptoms and eosinophils in the esophagus on dietary exclusion of cow's milk [60, 61] or with oral steroids [58, 61], both suggesting a pathoetiologic role for eosinophils. The mucosal density of the eosinophils may be important, as noted above, in distinguishing between allergic esophagitis and EE. In addition to eosinophils, intraepithelial T lymphocytes, known as CINC or squiggle cells, have also been implicated as markers of reflux esophagitis (Fig. 79.6) [62, 63]. However, the degree of intraluminal esophageal acid exposure did not correlate well with the CINC count in one study in children, and the authors use this fact to question the day-to-day reliability of pH metry in defining the extent of reflux in children [45]. In adults, such cells are of memory phenotype and display activation markers [63], although little is known of their pediatric equivalents. The finding of mucosal mast cells may also help to differentiate GER from CMP-associated esophagitis, but there is considerable overlap with the presence of eosinophils [64]. Neutrophils also indicate a degree of inflammation [65], and actual numbers of eosinophils and/or neutrophils per most-involved HPF have been used to indicate the severity of esophagitis [45]. Minimal histologic criteria are simultaneous occurrence of elongated papillae and basal zone hyperplasia. Moderate esophagitis is diagnosed if there is ingrowth of vessels in the papillae, and 1–19

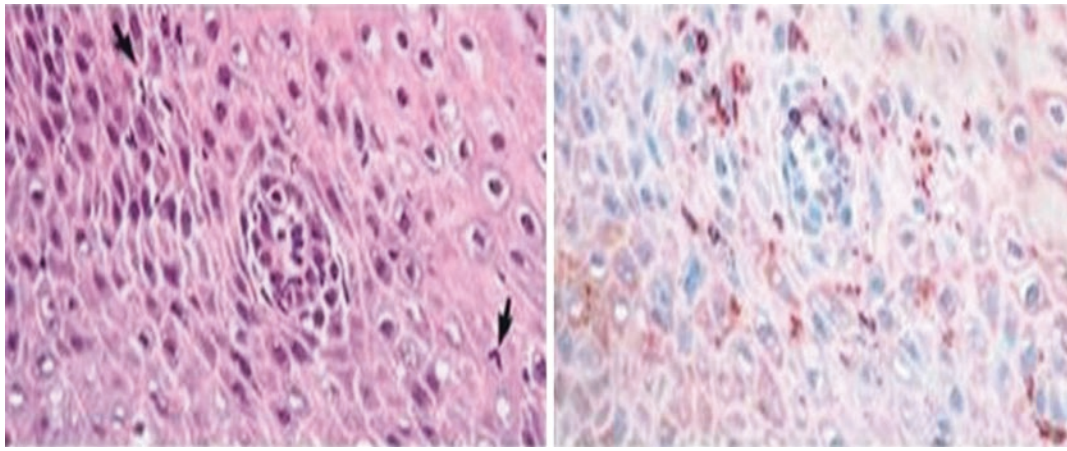

Fig. 79.6 Intraepithelial T lymphocytes in GORD biopsies and these are also known as squiggle cells

eosinophils/neutrophils are seen in the most-involved HPF. Severe esophagitis is diagnosed if more than 20 eosinophils/neutrophils are seen in the most-involved HPF. These criteria must now be taken in the context of eosinophilic esophagitis. However, the criteria established by European Society of Paediatric Gastroenterology Hepatology and Nutrition and displayed are probably the most robust to date [2].

The important point to realize is that correlation between macroscopic and histologic features is generally poor, partly because the esophagitis may be a patchy lesion but also because histologic esophagitis may exist when the esophagus is macroscopically normal [13]. This is not now merely academic because it does have the potential to direct therapy appropriately, for example, in the case of CMP allergy-associated esophagitis when a cow's milk exclusion diet is associated with a better outcome than use of antacid therapy alone, and it is suggested that up to 40% of cases of esophagitis may have CMP GI allergy as an etiologic factor [60, 61, 66].

Furthermore, with the advent of more complex diagnostic techniques such as immunohistochemistry and electron microscopy, the esophagus, which is apparently normal both macroscopically and histologically, may still yield diagnostic information. Standard endoscopic biopsy and histology do not reliably distinguish between, for instance, primary reflux esophagitis and the clinical entity of cow's milk-associated reflux esophagitis. Some differentiation from primary reflux has been suggested on the basis of esophageal pH testing pattern and α-lactoglobulin antibody response, although the former has not been substantiated by more than one center [61, 67].

Barrett's esophagus and premalignant or malignant esophageal pathology are dealt with in another chapter. Cytologic esophageal brushings may be helpful in such situations, as they are in candidal esophagitis [68].

Immunohistochemistry

A variety of immunohistochemical markers have been used to examine the esophageal mucosa. An increase in Ki-67, a proliferation marker, has been shown in the longer papillae seen in GER, suggesting increased cell turnover (Fig. 79.7). Basal focal distribution of CD4 lymphocytes showing expression of the activation markers CD25 and HLA-DR, together with upregulated epithelial HLA-DR expression, has also been reported [66]. Eotaxin is a recently described eosinophil-specific chemokine [69], and, despite the mild histologic abnormality in CMP-associated esophagitis, an increased expression of eotaxin colocalized with activated T lymphocytes to the basal and papillary epithelium has been shown, distinguishing this from primary reflux esophagitis (see Fig. 79.8) [66]. Inhibitory neurotransmitter production is integral to LES relaxation, and the nonadrenergic,

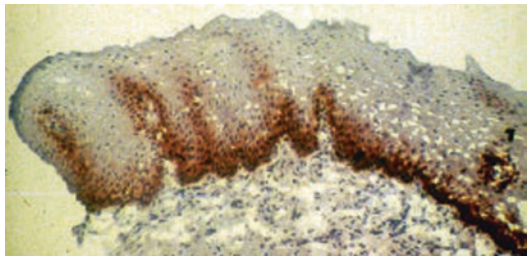

Fig. 79.7 The brown stain indicates Ki67 which is a marker of cell turnover and is upregulated here indicating that in reflux the cells are damaged in the epithelium and require more rapid replacement

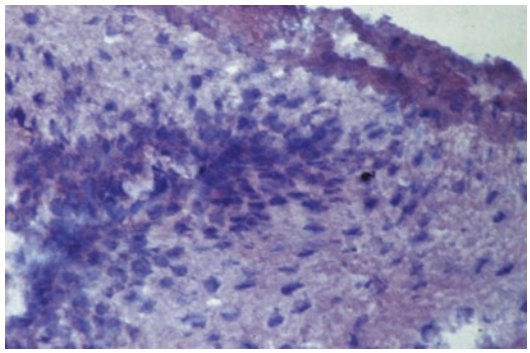

Fig. 79.8 Increased expression of eotaxin colocalized with activated T lymphocytes to the basal and papillary epithelium typical of allergic type esophageal changes often seen in conjunction with reflux

noncholinergic neurotransmitter NO has received recent attention in human studies [70, 71]. Increased esophageal expression of iNOS has also been noted [72, 73], although in another study, it was not upregulated in the inflamed pediatric esophagus [74]. Because NO is a powerful smooth muscle relaxant, it is interesting to speculate whether inflammation-induced iNOS may play a role in LES relaxation, leading to more reflux and hence worse inflammation, and so on. An exciting development is that of confocal endo-microscopy in which real-time images of the cell ultrastructure can be obtained at endoscopy, which is dealt with below.

Hence, techniques such as immunohistochemistry will allow better comprehension of the pathophysiology of esophageal pathology in the near future and already allow a diagnostic distinction to be drawn between etiologies.

Electron Microscopy

Electron microscopy has demonstrated the ultrastructural changes associated with esophagitis, adding to our comprehension of the lesion. Stratified squamous non-keratinizing epithelium line the mucosa, and the surface is composed of large flat cells displaying a regular pattern of parallel microridges 200 nm in thickness. Three layers are visible by transmission electron microscopy: (1) the basal layer, composed of polygonal cells with a high nucleus-to-cytoplasm ratio; (2) the intermediate layer, composed of large prickle cells; and (3) the superficial layer, composed of flattened cells. Three grades of ultrastructural changes in esophagitis in children have been identified: grade I, irregular microridges and reduced intercellular junctions; grade II, of the superficial epithelium only, microvilli instead of microridges that, when present, are distorted, and extruding cells with degeneration and interruptions of the cell membrane; lymphocytes and monocytes occupy the large intercellular spaces in the intermediate layer, and the basal layer is thickened; and grade III, microerosive cytopathy, loss of superficial layer microridges with crater-like erosions and abundant cell debris. Degenerating cells are seen in all three layers. Reduced numbers of desmosomes and large intercellular spaces containing lympho-monocytes are seen. Ultrastructural damage to nuclei, nucleoli, Golgi complex, and endoplasmic reticulum is seen. Activation of eosinophils by electron microscopic criteria has helped in the distinction of GER and CMP-associated esophagitis [64]. Hence, a more compelling case can be made for biopsy than previously.

Upper GI endoscopy allows direct visual examination of the esophageal mucosa; mucosal biopsies enable evaluation of the microscopic anatomy [10]. Macroscopic lesions associated with GERD include esophagitis, erosions, exudate, ulcers, strictures, hiatal hernia, areas of possible esophageal metaplasia, and polyps. While endoscopy can detect strictures, subtle degrees of narrowing may be better shown on barium contrast study, during which the esophagus can

be distended with various techniques, such as a radiopaque pill, barium-soaked bread, or marshmallows. Malrotation and achalasia cannot be diagnosed by endoscopy. These and other anatomic and motility disorders of the esophagus are better evaluated by barium radiology or motility studies.

Endo-ultrasound

There is little or no role for endo-ultrasound in the evaluation of reflux esophagitis, although Fox et al. have used this technique to identify that eosinophilic esophagitis is a transmural condition [75].

Confocal Endo-microscopy

The endoscopic procedure using the confocal endomicroscope (EC3870CILK; Pentax, Tokyo, Japan) has been well described [76]. Following duodenal intubation, 0.05–0.1 ml/kg of 10 % fluorescein sodium is administered intravenously and flushed adequately with normal saline. On withdrawing the scope to the lower end of the esophagus, acriflavine 0.05 % is sprayed on the surface of the esophageal mucosa using a spray catheter. CLE image acquisition is performed by placing the tip of the endoscope in direct contact with the surface of the esophageal mucosa (Fig. 79.9). Using gentle suction to stabilize the mucosa, image acquisition and focal plane z-axis scanning depth is then actuated using two discrete hand-piece control buttons (Fig. 79.10). The imaging depth below the tissue surface can be dynamically controlled by the operator. With each deeper plane, the focal plane of the confocal microscope moves by 4 μm and consequently the image obtained is approximately 4 μm deeper than the previous one. Consecutive confocal images are then obtained from the esophagus sequentially at different planes from the surface to the maximum permissible depth (Fig. 79.11). The S-P distance in μm is calculated by counting the number of images obtained from the surface until the first capillary loop is first detected and multiplying by a factor of 4.

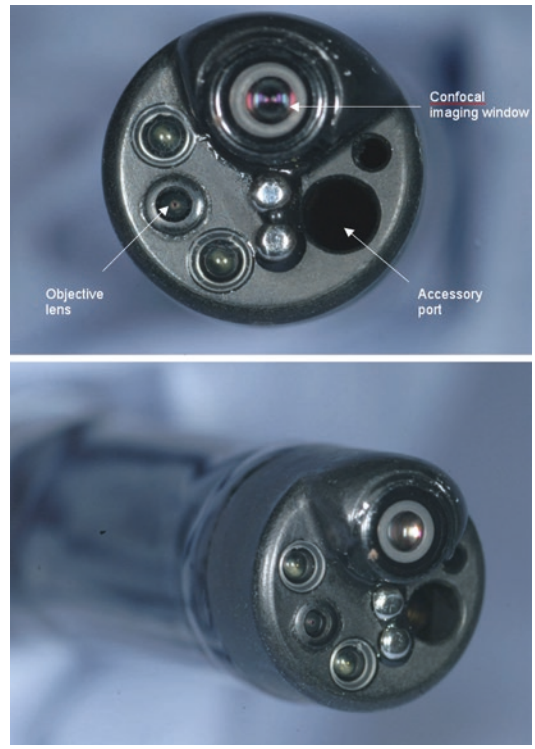

Fig. 79.9 The tip of a confocal endo-microscope

Fig. 79.10 The endoscope handle with all features demonstrated

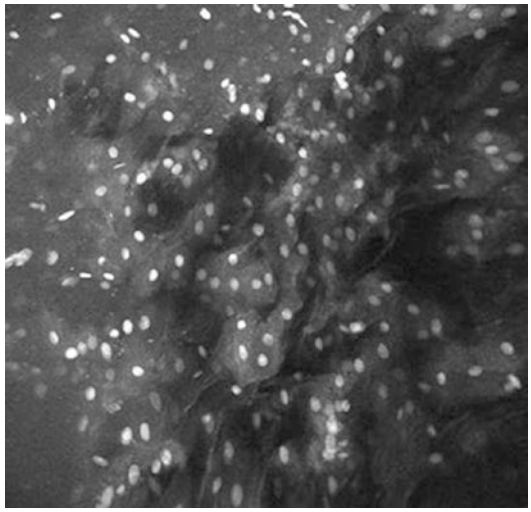

Fig. 79.11 The esophageal mucosal surface visualized with confocal endo-microscopy 'en-face' – nuclei are the white dots and the stratified epithelial cells can be clearly seen

One small pilot study indicates that the epithelial surface to papillary tip distance (which would be less in reflux if papillae were elongated in reflux), when measured with respect to the denominator of patient height, was indeed smaller in reflux suffering patients than in controls. Furthermore EE patients had a longest epithelium-papilla tip distance as has been shown on endo-ultrasound [77].

The major advantage of the confocal method is the capacity to make a real-time in vivo diagnosis of reflux-related esophageal change associated with esophagitis. One limitation is the reliance on one particular feature (papillary elongation) in arriving at a diagnosis, and may decrease the number of biopsies needed, and as a corollary allow targeting of biopsies for histology. While this method may not be the most accurate and definitive method to diagnose esophagitis, it may add to the diagnostic armamentarium of reflux-related esophagitis, and further studies on GERD and other pathologies such as eosinophilic esophagitis are needed.

This Chapter has not dealt with Barrett's esophagus which can be reviewed elsewhere.

In summary, endoscopy need not be utilized in the diagnosis of reflux-related esophagitis, but where it comes into its own realm is in the differentiation against other pathologies especially eosinophilic esophagitis – indeed this may, in years to come, provide the major justification for endoscopy and biopsy in children presenting with reflux-like symptoms and especially in those with dysphagia. There remains little or no reason to subject infants to endoscopic assessment to determine reflux-related esophagitis or reflux-related changes on histology alone, unless assessment of disease control on treatment in combination with pH or combined pH-impedance monitoring is contemplated. More sophisticated technologies may allow smart targeting of biopsies with attendant decrease in biopsy numbers and associated financial saving.

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Barium Contrast Radiography and Scintigraphy

80

Rossella Turco, Dario Ummarino, and Annamaria Staiano

Introduction

Several tests have been advocated to evaluate patients with suspected gastroesophageal reflux disease (GERD), including endoscopy, manometry, barium contrast radiography, scintigraphy, 24-h pH monitoring, and combined pH-metry and multichannel intraluminal impedance [51]. Barium contrast radiography was proposed in the investigation of GER in order to document the retrograde flow of gastric content. This technique has been proposed to be useful for the evaluation of motility and for morphologic abnormalities of the esophagus. Scintigraphy utilizes milk or liquid-labeled ^{99m} technetium feeds to evaluate gastric emptying and possible microaspiration. This nuclear scan evaluates only postprandial reflux and is not able to correlate refluxes with gastric pH. A lack of standardized technique and the absence of age-specific values reduce the accuracy of this test. According to the last NASPGHAN and ESPGHAN guidelines on GERD, both techniques are not useful in the routine diagnosis of GERD. The main reasons are:

– The small duration of the exam may show only an isolated episode of reflux which cannot be considered significant [54].
– The sensitivity and the specificity of barium contrast radiography and scintigraphy are 29 % and 15 %, and 21 % and 83 %, respectively. These values are definitely very low compared with pH-metry sensitivity (86 %) and specificity (100 %) [25, 50, 54].

Barium Contrast Radiography

Barium contrast radiography, or gastrointestinal series (GI series), is a noninvasive technique used for the evaluation of upper gastrointestinal disorders. This technique is usually executed as a multiphase examination that includes various steps such as the timed barium swallow, the oropharyngeal phase, the motility phase, the distended or single-contrast phase, and then an attempt at reflux identification. The upper GI series can be performed in different views:

1. Double-contrast view using a high-density barium suspension.
2. Single-contrast view using low-density barium suspension.
3. Mucosal relief view using higher or low density of barium suspension [29, 30].

These different techniques are associated with different positions, allowing the radiologist the ability to detect specific abnormalities or disease processes. With barium contrast radiography, it is only possible to evaluate malformations in the GI tract. Historically it has been used to

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try to demonstrate the presence of ulcers, strictures, or other abnormalities of the mucosa. At the same time, it can monitor a retrograde flow of the barium from the stomach to the esophagus that could indicate a reflux of gastric content (Fig. 80.1). Bilious vomiting, protracted vomiting, feeding difficulty or dysphagia, poor weight gain or weight loss, and assessment of the status of previous fundoplication are the major indications of barium contrast radiography in children. The upper GI series is also utilized for assessing swallowing disorders and oropharyngeal aspiration in children and is usually termed a "videofluoroscopy" in these situations [4].

Use of the Upper GI Series in Diagnosis of GERD

The effectiveness and importance of reflux identification during barium studies have been questioned by many authors [35]. An upper GI series can identify a single reflux event (Figs. 80.2 and 80.3), but conflicting data exist about the possible correlation between the size and height of reflux detected by barium contrast radiography and the presence of GER/GERD. Christiansen et al. found a positive correlation between the level of reflux on barium studies and the proximal extent of reflux esophagitis on microscopic examination of endoscopic biopsy specimens from the esophagus [11]. Moreover, Pan et al. comparing the findings on 24-h pH-metry, with those of barium contrast radiography of 28 patients, observed that patients with massive reflux episodes on barium contrast radiography had pathologic acid reflux on pH monitoring [37]. On the other hand, it has been recently established that no correlation exists between the height of reflux and esophageal/extraesophageal symptoms, prognosis, or the natural history of GERD [6]. Indeed, reviewing various data reported in the literature, we noted a broad agreement not to consider barium contrast radiography as a useful tool in the diagnosis of GERD because of its low sensitivity and specificity. In a review of ten previously published studies, Ott found that only 204 (35 %) of 587 patients with proven reflux had a GERD detected on GI series, showing a lower sensitivity of this technique compared to 24-h pH-metry [35]. In the literature, several studies, concerning the attempt to demonstrate higher barium contrast radiography sensitivity and specificity, are reported. Thompson

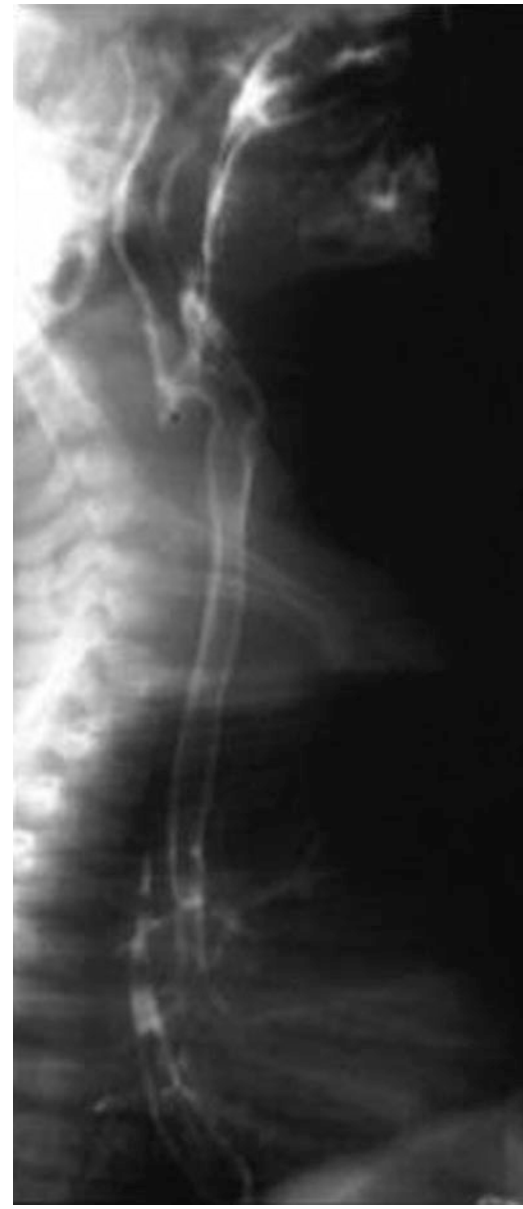

Fig. 80.1 A retrograde flow of barium in pharynx due to an incoordination of swallowing evaluate trough barium contrast radiography (Photographs made available by Department of Radiology, University of Naples Federico II, courtesy of Hana Dolenzalova, M.D.)

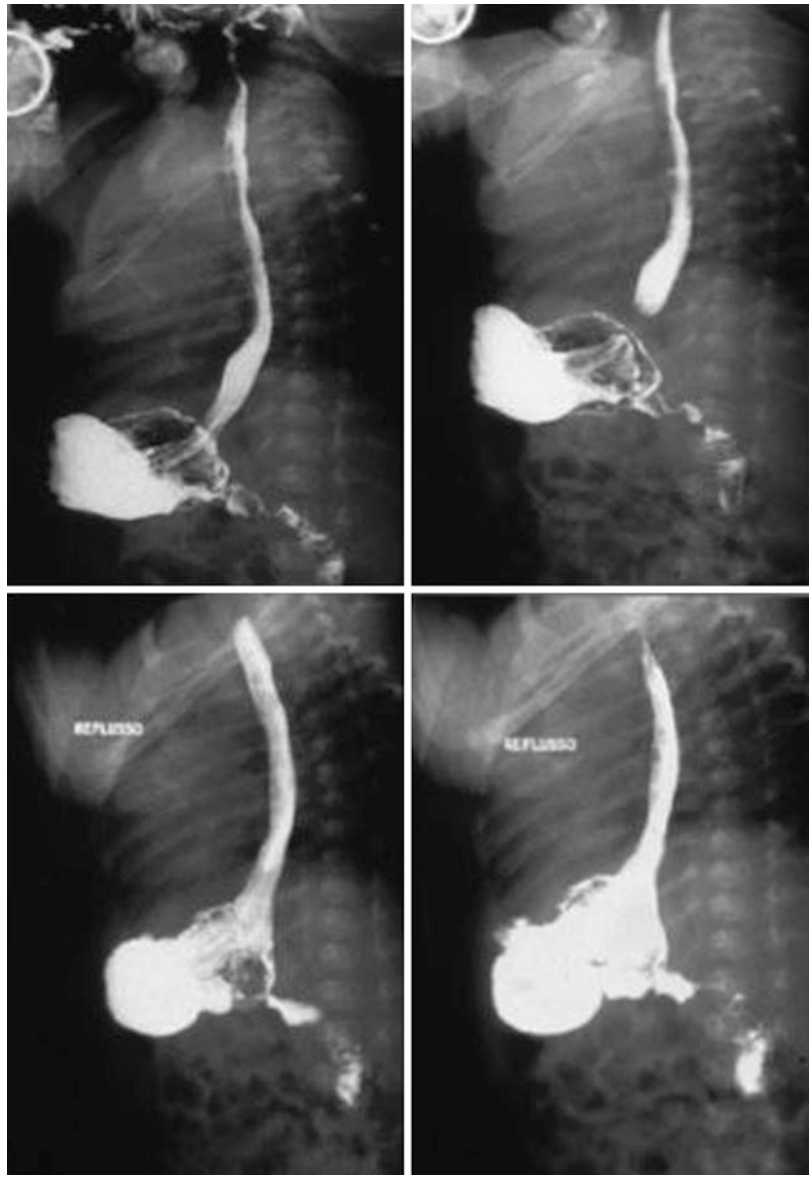

Fig. 80.2 Gastro-esophageal reflux (Photographs made available by Department of Radiology, University of Naples Federico II, courtesy of Hana Dolenzalova, M.D.)

et al. [46] studied 117 patients with clinical findings suggestive of reflux by using GI series and pH-metry. Seventy (59 %) had a positive pH-metry while 47 (41 %) had a negative one. They found, according to previous data, that using provocative maneuvers, including abdominal compression, the Valsalva maneuver, positional changes, leg lifting, coughing, and water siphon test, induced an enhancement of sensitivity (44–92 %), with decrease in specificity (0–75 %) [6, 17, 46]. In addition, it has been observed that the upper GI series is not indicated for infants less than 1 year of age because it has a specificity of 50 % and a sensitivity of 29 % when compared with 24-h pH-metry [1].

Several reasons could explain the limits of an upper GI series in detecting GER. One being that many infants have non-pathological, or physiological, reflux, producing false-positive results. Moreover the short duration of the upper GI series is the cause of false-negative results. Importantly the relatively high level of radiation

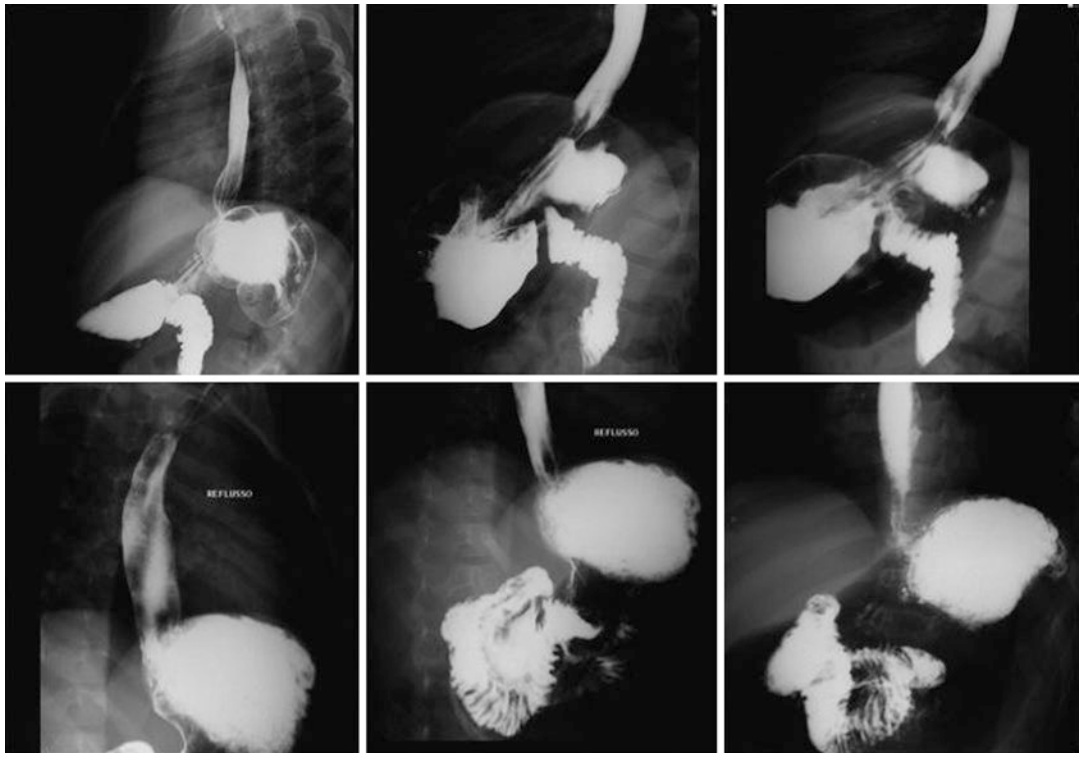

Fig. 80.3 Gastroesophageal reflux (Photographs made available by Department of Radiology, University of Naples Federico II, courtesy of Hana Dolenzalova, M.D.)

received by the child during a barium contrast examination is another important limitation for the use of this technique which should be considered in the diagnostic approach of a child with GERD suspicion [53]. For all the abovementioned reasons, GI series is not of value for the routine diagnosis of GERD, but its possible indications in GER are confined to the evaluation of upper GI anatomical abnormalities such as esophageal strictures, hiatal herniae, achalasia, tracheoesophageal fistulae, intestinal malrotations, or pyloric stenoses, which may be considered in the differential diagnosis of infants and children with symptoms suggestive of GERD.

The upper GI series is reported by some to have a sensitivity of 90 % in the detection of reflux esophagitis. The early manifestations of reflux esophagitis are said to be represented by a fine nodular or granular appearance with poorly defined radiolucencies that fade peripherally for the edema and inflammation of mucosa [10, 31] (Fig. 80.4). In patients with severe reflux, barium contrast radiography may, it is said, show the evidence of small ulcers, erosions, or strictures of the esophagus, but this remains highly dubious and generally thought to be without substance or reliability [43]. The classic signs of Barrett's esophagus instead are found only in 5–10 % of all patients, and this modality remains extremely suspect in this essentially histological diagnosis [13, 21, 22]. Achalasia is characterized by the incomplete relaxation of the lower oesophageal sphincter (LES) and the absence of esophageal peristalsis which causes a functional obstruction of the distal esophagus. Using barium contrast radiography, the esophagus appears dilated with a tapered beak-like narrowing near the gastroesophageal junction [28, 29, 36, 44] (Fig. 80.5).

Hiatal herniae consist of the herniation of parts of the abdominal contents through the oesophageal hiatus of the diaphragm. The relationship between esophagitis and hiatal hernia

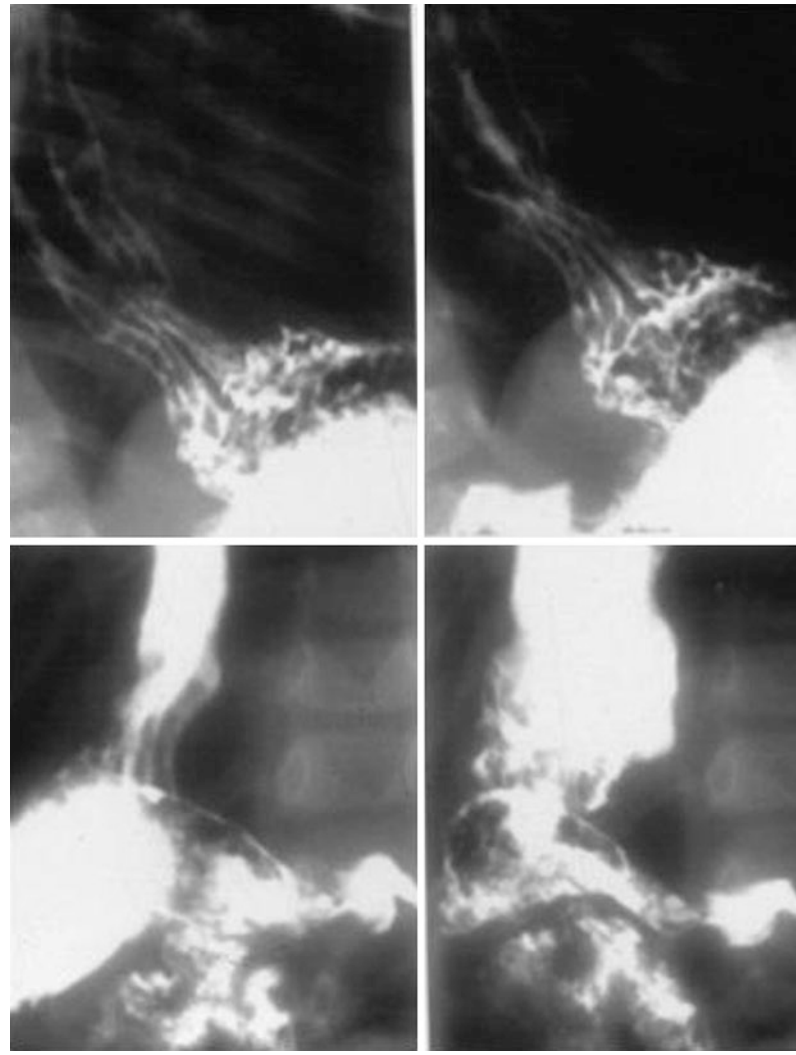

Fig. 80.4 Early esophagitis. It is possible to note the edema of the mucosa with an increasing of the esophageal folds (Photographs made available by Department of Radiology, University of Naples Federico II, courtesy of Hana Dolenzalova, M.D.)

has been established for many years both in children and in adults. It is known that in the presence of a hiatal hernia, all of the antireflux barriers at the LES (including crural support, intra-abdominal segment, and angle of His) are compromised [7, 9, 33, 50], and transient LES relaxations also occur with greater frequency [33], increasing the possible onset of GERD. On the contrary the presence of erosive esophagitis by itself may promote esophageal shortening and consequent hiatal herniation, although this remains conjectural [33]. Both the presence and size of the hiatal hernia are important factors determining the GERD severity [8, 25]. As of now an upper GI series remains the most sensitive technique in the diagnosis of a hiatal hernia and its size.

Intestinal malrotation can occur as an acute abdomen or as a recurrent episode of abdominal pain and/or vomit. An intermittent volvulus or a duodenum compression due to Ladd's band or to adhesions of the ileum or colon can explain this symptomatology. GI radiography, especially barium contrast radiography, is useful for the diagnosis of this malformation. It remains the most sensitive and specific technique for the diagnosis of malrotation, and the presence of bile-stained vomiting is categorically not needed for the suspicion of this diagnosis – in other words any child with intermittent abdominal pain/vomiting should

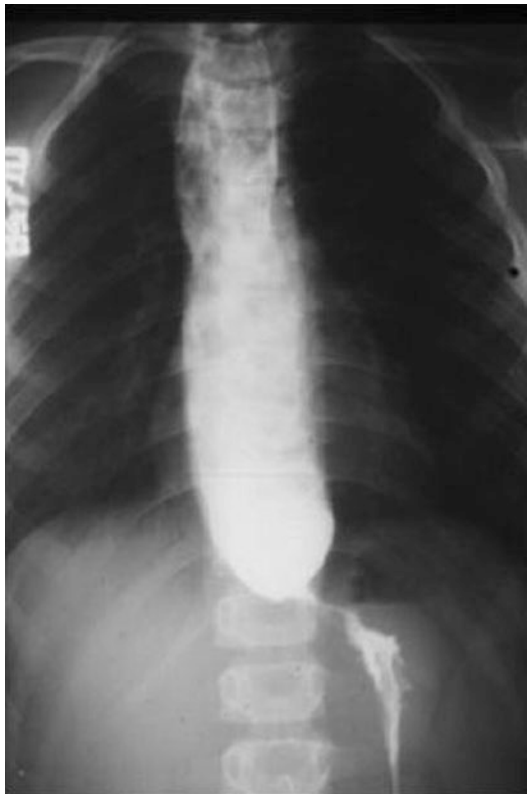

Fig. 80.5 An image of esophageal achalasia (Photographs made available by Department of Radiology, University of Naples Federico II, courtesy of Hana Dolenzalova, M.D.)

have this diagnosis borne in mind by their doctor. Anything less than a high index of suspicion for this potentially devastating condition with volvulus and small bowel necrosis leading to short bowel syndrome and a life dependent on parenteral nutrition is inadvisable.

Esophageal strictures can be congenital or acquired. They can be caused by or associated with GERD, esophagitis, dysfunctional LES, disordered motility, hiatal hernia, surgical anastomosis, infections, and caustic ingestion (Fig. 80.6). GI series is the gold standard to diagnosis of the majority of esophageal strictures.

Classically, infants with hypertrophic pyloric stenosis have non-bilious vomiting or regurgitation which sometimes can be interpreted as consequences of GERD. In these cases an upper GI series may show an elongated pyloric canal, a prominence of the pyloric muscle in the gastric antrum (the so-called *shoulder sign*), and parallel barium streaks in the narrowed canal which determine the so-called *double track sign*. Nowadays ultrasound is considered the gold standard for pyloric stenosis diagnosis.

Scintigraphy

First Kazem in 1972 tried to develop a new technique, scintigraphy, for the evaluation of GI function [27], and since that time it has been applied to a variety of pathophysiologic conditions. Esophageal scintigraphy, which was introduced in 1976 [16] as a diagnostic tool to try to evaluate GER, seemed to be a potentially accurate and noninvasive technique to diagnose and quantify reflux. However, the lack of a standardized technique for the performance and the interpretation of this test and the absence of age-specific values are the main reasons to explain why the importance of scintigraphy in the diagnosis of GER has decreased. Nevertheless, several studies have been conducted to estimate the role of scintigraphy for the evaluation of upper GI function, especially the ability to detect gastroesophageal reflux, both in pediatric and adult populations. Scintigraphic evaluation of children with suspected GERD is performed with several approaches using caloric liquid or solid meals labeled with ^{99m} technetium (Tc), appropriate to the patient's age. A gamma camera equipped with an adequate collimator placed in front of the recumbent patient is needed to obtain a dynamic study of the esophagogastric region and lungs. Standard protocols and guidelines on GERD scintigraphy require a 60-min dynamic acquisition during which reflux episodes with their duration, extension, and aspiration are recorded. Since transient reflux can rapidly dissolve, a rapid imaging (10–20 s/images) is needed. At the end of dynamic acquisition, 5-min static images of the anterior and posterior lung fields are acquired. Reyhan et al., comparing the posterior dynamic imaging with the anterior imaging in the evaluation of children with GERD, showed that posterior imaging was superior to anterior imaging, being more comfortable and with less motion

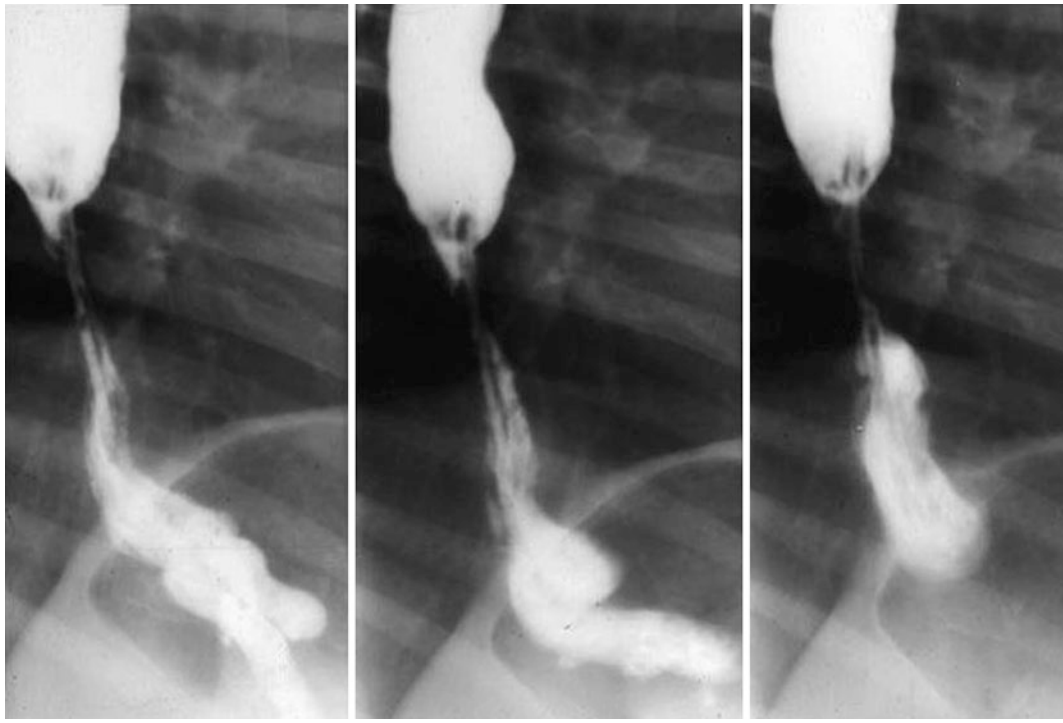

Fig. 80.6 A stricture of the distal esophagus due to an advance esophagitis (Photographs made available by Department of Radiology, University of Naples Federico II, courtesy of Hana Dolenzalova, M.D.)

artifacts, especially for infants and anxious children [41]. Finally gastroesophageal reflux can be described using different indices, which usually consider the volume of each episode, the frequency of the episodes, and the rate of reflux clearance from the esophagus.

Scintigraphy in Diagnosis of Upper Gastrointestinal Diseases

Although gastroesophageal scintigraphy is a practical and noninvasive technique with low levels of radiation exposure for children compared to barium, its significance in diagnosing GER, it is limited by the failure of scintigraphy to achieve a sensitivity similar to that of other tests, particularly esophageal pH monitoring. Sensitivity and specificity of a 1-h scintigraphy for the diagnosis of GERD are 15–59 % and 83–100 %, respectively, when compared with 24-h pH-metry [2, 3, 14, 42, 47]. Seibert et al. [42] first reported a sensitivity and a specificity of 79 % and 93 %, respectively, when comparing gastroesophageal scintigraphy to 24-h pH-metry, analyzing 49 infants and children with suspected GER. Tolia et al. [47] comparing esophageal pH-metry with gastroesophageal scintigraphy observed that the incidence of GER was 69.5 % by pH-metry and 66.0 % by gastroesophageal scintigraphy in symptomatic infants of less than 1 year of age. Vandenplas et al. also performed simultaneous pH monitoring and scintigraphy in children and found that among 123 separate reflux episodes detected, only six were recorded by both techniques [3]. Gastroesophageal scintigraphy evaluates only postprandial reflux and it is not able to correlate refluxes with gastric pH. This offers certain advantages over pH monitoring because gastric acidity may be neutralized by food, especially milk, in the immediate postprandial period, making pH studies unreliable [49]. Scintigraphy may be particularly useful in patients with GERD suspicion, but with negative result at pH monitoring. Gastroesophageal reflux can be acid, nonacid,

or weakly acid. GERD-associated respiratory problems seem to be related to nonacid refluxes which can be missed by intraesophageal pH monitoring. Studies using multichannel intraluminal impedance/pH-metry have shown that sensitivity of pH monitoring for the detection of retrograde bolus reflux is only 8%, and up to 90% of refluxes may be missed since they are neutral or slightly alkaline [34, 54]. It is known that in infants, only 16% of all reflux episodes associated with breathing abnormalities and oxygen desaturation were detected by pH monitoring [57], and only 22% of apnea-associated reflux episodes were acid and thus detected by pH monitoring [56]. According to the previous study, Thomas et al. [55] studied 126 children aged 6 months to 6 years and found that 70% of them had no gastrointestinal symptoms suggestive of GERD despite scintigraphic evidence of reflux. Karaman et al. using radionuclide scintigraphy showed a 21.1% incidence of GERD in 74 children with recurrent wheezing [45]. These data confirmed a possible use of gastroesophageal scintigraphy for the diagnosis of GERD in patients with atypical GERD symptoms in which gastric pH could be within the physiologic range. A recent study [26] assessed the validity of GERD scintigraphy in children older than 7 years demonstrating that of 75 patients who presented with chronic cough, 65 (86%) had GERD on scintigraphy. Nevertheless gastroesophageal scintigraphy has a relatively low sensitivity to analyze microaspiration [5, 15, 19] so that a negative test does not exclude the possibility of infrequently occurring aspiration [19]. Evidence of pulmonary aspiration may be detected during a 1-h scintigraphic study or on images obtained up to 24 h after administration of the radionuclide [16]. One study of children with refractory respiratory symptoms found that half had scintigraphic evidence of pulmonary aspiration [19]. However, aspiration of both gastric contents and saliva also occurs in healthy adults during deep sleep [17, 40]. Scintigraphy can provide information about gastric emptying. It is known that delayed gastric emptying may predispose to GERD in adults [32] and in children [20, 24]. Gastric emptying studies have shown prolonged half-emptying times in children with GERD. Gastric emptying scintigraphy has become a complementary part of routine gastroesophageal reflux scintigraphy, and even if tests of gastric emptying are not a part of the routine examination of patients with suspected GERD, they may be important when symptoms suggest gastric retention or when gastrostomy placement is needed [12, 23, 38, 52]. Respect to barium studies, scintigraphy is unable to delineate anatomic features, such as hiatus hernia, frequently associated to GERD, but its radiation exposure is considerably less than with barium studies. In addition, it has the advantage of allowing long periods of observation to detect refluxes. In a study on 35 children with a suspicion of GERD, comparing barium studies and scintigraphy with endoscopic findings, authors found that scintigraphy was more accurate to estimate reflux episodes than barium studies [18]. However, there was no significant relationship between scintigraphic study and endoscopic findings. In conclusion these data confirm the notion that even if scintigraphy can explore some important aspects of GERD, it is not recommended in the routine diagnosis and management of this disease in infants and children [39, 48].

Conclusions

According to the last evidence-based NASPGHAN and ESPGHAN guidelines on the diagnosis of GERD, we recommend:

1. The upper GI series is not useful for the diagnosis of GERD, but is useful for the diagnosis of anatomic abnormalities (Quality of Evidence B).
2. Scintigraphy could have a role in the diagnosis of aspiration in patients with chronic refractory respiratory symptoms, but the technique is not recommended in patients with other potentially gastroesophageal reflux-related symptoms (Quality of Evidence B).

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Assessment of GERD: Ultrasound

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Ahmed Sarkhy

Ultrasound (US) or sonography has been utilized for many years in different fields of diagnostic imaging, including GERD diagnosis mainly due to pragmatic reasons: low cost, wide availability, and relative noninvasiveness [1–4].

US study allows for direct, real-time visualization of the gastroesophageal junction (GEJ) and of the retrograde movement of reflux events. In addition, it can detect anatomical defects such as hiatus hernia and indirectly measure the lower esophageal sphincter (LES) length. Color Doppler ultrasound was also added to the standard US study which has been reported to increase its sensitivity in detecting GER events [5–8]. Furthermore, recent studies started to use endoscopic US in the measurement of the esophageal wall thickness to assess esophageal inflammation secondary to GERD; however, this is still an evolving technique [9, 10]. Using specific criteria, Tomita et al. conducted a study to correlate the abdominal US findings with endoscopy findings in adult patients with erosive GERD ($n=37$) and nonerosive GERD ($n=24$) compared to a control group without GERD ($n=32$). All of the participants had upper gastrointestinal endoscopy. The US operator was not aware of the endoscopy findings. GERD was diagnosed when two or more of these items were positive: (i) lower esophageal thickness (> or = 5 mm), (ii) abnormal architecture of the esophageal wall, and (iii) the presence of reflux. The thickness in erosive GERD was reported to be significantly greater than that in nonerosive reflux disease (NERD) patients and controls. Sensitivity, specificity, and accuracy of abdominal US diagnosis for erosive GERD and NERD (control participants worked as a reference group) were 84.6%, 25%, 91.1% and 91.1%, 89.4%, and 63.8%, respectively [11].

Though US is a cheap and noninvasive diagnostic tool, it does have several limitations in GERD diagnosis. These include its inability to depict the intrathoracic esophagus which limits the study to a short segment of the distal esophagus; another limitation is that it provides only a snap shot picture of the fluid movement across a short period of time. However, the major limitation is that it does not provide any information about the nature of the refluxate (acidic or not) and it does not correlate well with the reflux index of acid reflux as measured by pH monitoring [8, 12]. Jang et al. conducted a study where contrast color Doppler US (CDUS) and 24-h esophageal pH monitoring were performed in 54 children (2 months to 10 years). The authors demonstrated that CDUS had a high sensitivity (95.5%) for diagnosing the presence of GER but a very low specificity (11.0%), with a positive predictive value of 84.3% and a negative

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predictive value of 33.3 %. However, they did not find a statistically significant correlation between the frequencies of GER detected on CDUS and the reflux index detected on pH monitoring. In addition, there was no correlation between the reflux grades on CDUS and that measured by pH monitoring [8].

The conclusion from different studies that demonstrated the utility of US in GERD diagnosis is that US is difficult to transfer to reliable clinical application because of several methodological issues among some of these studies. Namely, some studies did not compare US findings to a gold standard test such as the pH metry/impedance study – in fact some of these studies compare it to barium swallow which is neither sensitive nor specific for GER/GERD diagnosis. In some of these studies, the GER/GERD diagnosis had variable denominators for diagnosis which were therefore not comparable [13]. Others tried to measure an age-standardized abdominal esophagus length in children without taking into consideration the effect of the weight/height of the children, which could be a potential confounding factor on these measurements and probably therefore would affect its clinical application [14]. Recording of longitudinal muscle contraction using catheter-based, intraluminal ultrasound imaging technique represents another technological advance – this is dealt with elsewhere.

In summary, though US is a noninvasive and readily available diagnostic tool, its role in GER/GERD diagnosis is very limited. Providing information about the presence/absence of GER events and/or the volume/proximal extension of the reflux episodes is insufficient without having the information about the reflux index provided – typically by a pH/impedance monitoring study. The current combined North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) clinical practice guidelines do not recommend using US for the routine diagnosis of GERD [15]. It should be remembered that endo-ultrasound may be of benefit in defining other pathologies of the esophagus such as eosinophilic esophagitis and structural abnormalities such as diverticuli or strictures – these various pathologies as related to US will be dealt with in the relevant chapters.

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Ear, Lung, and Esophageal Fluid Evaluation in GER Diagnosis

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David J. Rawat

Introduction

The upper aerodigestive tract, which consists of the nose, mouth, pharynx, larynx, and the esophagus, allows for the passage of air and food. In children, extraesophageal ENT manifestations of GER may affect the ears, paranasal sinuses, lungs, and oral cavity. These structures form one of the most complex neuromuscular systems of the body providing the structural and dynamic components for swallowing, respiration, and speech. Historically, the extraesophageal or supra-esophageal manifestations of GERD had received more attention from our ENT and respiratory colleagues. However, better understanding and appreciation of pathophysiological processes and concordant clinical importance of the esophagus especially in relation to these supra-esophageal manifestations have resulted in a revival of interest. Fortunately, techniques to study esophageal motor patterns have improved tremendously over the years. From the side-hole sensor to Dent sleeve sensor to the current electronic sleeve sensors, life has been made much simpler for clinicians and researchers alike. State-of-the-art catheters equipped with 36 solid-state transducers that are circumferentially sensitive and span the entire length of the pharynx, esophagus, and proximal stomach have replaced infusion manometry recording techniques. Topographical visualization of pressure waves recorded by closely spaced sensors and high-resolution manometry (HRM) with seamless color pressure plots using computer algorithms with linear interpolation of pressure between closely spaced transducers along the length of the esophagus represent a significant advance. Recording of longitudinal muscle contraction using catheter-based, intraluminal ultrasound imaging technique represents another technological advance. The ontogeny and motor disorders of the upper GI tract will be discussed in other chapters, but are ultimately integral to direction of flow and therefore relevant in the context of fluid evaluation.

The evaluation of fluids in the detection of disorders affecting the esophagus, larynx, lungs, and ears has been the focus of many researchers, clinicians, and scientists alike, largely because of the noninvasive nature of potential diagnostic tests, which is particularly attractive in pediatrics. This chapter will focus mainly on the evaluation of fluid involving the otolaryngeal and respiratory tracts and only briefly explore the esophagus which will be covered more extensively in some of the other chapters.

Evaluation of fluids of the aerodigestive tract requires recognition of the motor patterns of the foregut which ultimately influence the direction of flow of bolus passage. The three components required to produce mature esophageal motor

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function that are necessary are an integrated enteric and autonomic neural system, the inherent rhythmicity of smooth muscle, and the initial propagation of the peristaltic wave by the coordination of striated muscle.

Localized mechanical, or chemical, stimulation of the smooth muscle, or stretch of the muscularis externa, will elicit contraction above, and relaxation below, the point of stimulation. A stretch-sensitive neuron with connections in the myenteric plexus and chemosensitive or mechanosensitive neuron with connections in the submucosal plexus may both be stimulated, and this may result in ascending excitation (mediated by acetylcholine and substance P) and descending inhibition (mediated by vasoactive intestinal polypeptide and nitric oxide) of contraction of the smooth muscle of the muscularis externa. Stimuli to the mucosa evoke release of serotonin (5-HT) from enterochromaffin cells in the mucosa. Sensory neurons are simulated by 5-HT. The myenteric stretch receptors however respond directly to stretch. These sensory neurons then release intermediary substances, mainly calcitonin gene-related peptide, which acts on the neurons within the myenteric and submucosal plexuses thus controlling motility of that portion of the GI tract.

The neurohormonal influences on esophageal motility and lower esophageal sphincter (LES) pressure/function include:

Substance P (increases LES pressure and motility)
Vasoactive intestinal peptide (VIP) (inhibits esophageal tone)
Inducible nitric oxide synthase (iNOS) (may decrease resting tone and allow LES relaxation)

iNOS can be altered by inflammation. Inhibitory neurotransmitter production is integral to LES relaxation, and the non-adrenergic noncholinergic neurotransmitter nitric oxide (NO) has received attention in animal [1] and human studies [2, 3]. Vasoactive intestinal polypeptide (VIP) is another candidate undergoing investigation, and the importance of the ontogeny of neuropeptides in the human fetus and infant is becoming increasingly apparent [4]. The complex interaction of the neuroenteric-hormonal axis has particularly been the focus of recent work in such conditions as allergic and eosinophilic esophagitis (EE) suggesting a role for other inflammatory-induced mediators in the pathogenesis of the associated LES dysfunction (e.g., interleukin 5, eotaxin, eosinophil-derived neurotoxin) [5, 6]. It should be mentioned that the central nervous system may play a part in overall esophageal motility, as evidenced by the disorder to normal esophageal peristalsis which occurs in neonates with peripartum cerebral insults leading to cerebral palsy.

The process of swallowing consists of four phases for liquids and solids alike:

Oral preparatory
Oral
Pharyngeal
Esophageal

Functional real-time swallowing is best studied using videofluoroscopy. The pharyngeal phase consists of several closely coordinated functional elements that make up the complex motor event referred to as the swallow response. Pharyngeal swallows are initiated in an ordered, sequential pattern in response to stimulation by food or sensory stimulation to the medullary swallowing center (i.e., nucleus tractus solitarius and ventromedial reticular formation) via cranial nerves V, IX, and X [7]. In the older child or adult, the upper pharynx and the soft palate close against the posterior pharynx as the food bolus is propelled by the tongue into the pharynx, sealing the nasal cavity. Closure of the larynx protects against airway penetration of the bolus. Simultaneously there is complete and automatic closure of the glottis, and the epiglottis is brought down over the glottis hence deflecting the bolus laterally and posteriorly toward the upper esophageal sphincter (UES). The upper esophageal sphincter opens, and peristaltic contractions of the pharyngeal constrictor muscles drive the bolus through the pharynx, past the displaced, closed larynx into the esophagus. With high-speed videofluoroscopy four sequential events associated with laryngeal closure have been noted:

Adduction of the true vocal cords associated with the horizontal approximation of the arytenoid cartilages, vertical approximation of the arytenoids to the base of the epiglottis, laryngeal elevation, and epiglottic descent.

The other major function of the laryngopharyngeal space is in eliciting a protective cough reflex precipitated by a number of vagally mediated receptors (chemo-, thermoreceptor, etc.) which detect the presence of potentially damaging noxious stimuli and cause laryngeal closure and a cough. This is becoming increasingly important to gastroenterologists as a phenomenon with the recent appreciation of the pathological importance of laryngopharyngeal reflux from the stomach (LPR) in symptoms such as recurrent cough, hoarseness, and dysphonia. An elevated resting pressure of the cricopharyngeal muscle is necessary to prevent pharyngeal penetration of the retrograde esophageal bolus. A normal pharyngeal swallow includes complete bolus transport through the pharynx and to the cricopharyngeus or upper esophageal sphincter (UES). The bolus must pass as the airway is protected from aspiration of swallowed material. Posterior transport through the pharynx is achieved by posterior tongue thrust, effective pharyngeal peristalsis, and upper esophageal sphincter opening [8, 9].

Nasopharyngeal reflux (NPR) can be considered a problem in both oral and pharyngeal phases of swallowing as it occurs at the transition between the two phases. The single most common oral phase occurrence of NPR occurs with a structural deficit, as a cleft palate. More than often NPR occurs when the palate or posterior pharyngeal wall do not oppose completely or in a timely manner relative to the transport of the bolus. In normal newborn infants, both premature and term, small amounts of NPR are considered normal [10]. However, NPR is a problem if it occurs repetitively or in amounts large enough to compromise nasal breathing. In rare instances a nasopharyngeal mass can interfere with palatal elevation, resulting in NPR. NPR may also be evident as a functional deficit when incoordination in pharyngeal phase timing occurs with neurologic deficits. Lack of velopharyngeal (VP) closure or incoordination of VP function at the onset of the pharyngeal phase results in material getting into nasal passages. Normally, the VP closure is brief just as the bolus passes the velopharyngeal port. When the pharyngeal swallow initiation is delayed and the barium pools in pharyngeal recesses, it is not uncommon for some of the bolus to get into the nasopharynx just prior to or during trigger of the swallow. NPR can also occur later in the pharyngeal phase when the velopharyngeal port has reopened if material cannot readily pass through the pharynx into the esophagus. NPR is more common with liquid than with other textures. In addition, NPR may be more common in infants who are fed in a semi-reclined position rather than an upright position.

An esophageal phase promptly follows each separate pharyngeal phase of the swallow when there is definite time delay between swallows. However, an immediate and complete inhibition of the esophageal phase is noted when a second pharyngeal swallow occurs while the bolus remains in the striated muscle segment of the esophagus. If the bolus from the first swallow is in the smooth muscle segment when the second swallow occurs, the initial bolus will progress for several seconds before dissipating. In contrast, the original swallow can alter the amplitude and velocity of subsequent swallows for as long as 10 s, depending on the bolus size [11]. A series of rapid swallows results in an inactive esophageal body and LES relaxation. The final swallow in the series will be followed by a solitary normal peristaltic wave that clears the esophagus of infants and adults [12].

As the correlation between extraesophageal reflux (EER) and airway and ear, nose, and throat (ENT) disease is gradually gaining recognition, so too is the need for new normative and diagnostic standards for EER relative to GER. We have also now come to accept that the sensitivity of airway and ENT tissues to gastric refluxate demands more stringent diagnostic criteria relative to GER. Moreover, the diagnosis of EER currently relies on the tools designed for the diagnosis GER. Such tools lack the sensitivity and reproducibility to detect the less frequent and mildly acidic reflux associated with EER disease.

This chapter will present a comprehensive review of the currently available diagnostic biomarkers that are utilized in the evaluation of ear, lung, and esophageal fluids concentrating mostly on the extraesophageal manifestations of GERD.

Ear Manifestations of Extraesophageal Reflux

Extraesophageal reflux disease (EERD) has long been implicated in the pathophysiology of otitis media (OM) in children. Ear manifestations, especially otitis media with effusion (OME), are nearly always exclusive to neonatal and infantile periods. This is because eustachian tube dysfunction is more frequent in children than adults. GER is now included among the risk factors for tube dysfunction due to large numbers of episodes of reflux in babies with respect to adults and due to prolonged lying in the supine position. The pathogenic mechanism would appear to be linked to contact of the rhinopharyngeal region with reflux material, and repeated exposure of the ciliate respiratory epithelium to pH 4 or less blocks the ciliary movement and subsequent mucus clearance. Hydrochloric acid and pepsin cause local inflammation, edema, and ulceration of the respiratory mucosa leading to loss of tube ventilatory function.

As with ear manifestations, those affecting the nose and sinuses are also frequent in children and are due to chronic inflammatory processes in the nasal and paranasal cavities. Considering the multifactorial etiology of rhinosinusitis, GER can be regarded as a cause of chronic pediatric rhinosinusitis [13]. The pathogenic mechanism by which acid reflux may affect the nose and sinuses is unclear. One possibility is its direct action on the nasal respiratory mucosa as occurs in the hypopharyngo-laryngeal district [14]. Excluding the hypothesis that reflux could reach the paranasal sinuses directly through the ostia, it may reach the rhinopharynx and posterior part of the nasal cavities where the only ostium communicating with the sphenoidal sinus is located. In this way, acid reflux could lead to nasal mucosal inflammation, edema, and obstruction of the osteo-meatal complex [15]. Another mechanism is hyperreactivity of the autonomic nervous system induced by reflux and leading to nasal edema and ostial obstruction [16]. The studies did not satisfactorily demonstrate these correlations. Although previously postulated, the relationship between GER and enlarged adenoids seems less likely. The question is whether reflux promotes an inflammatory process of adenoid tissue or whether the adenoids facilitate reflux by modifying intrathoracic inspiratory and expiratory pressures, thus favoring retrograde movement of gastric content in the esophagus.

Laryngeal Manifestations of Extraesophageal Reflux

Cherry and Margulies [17] were the first to recognize that GER could cause posterior laryngeal inflammation, contact ulceration, and granulation that improved with anti-reflux therapy.

The main set of laryngeal symptoms of GER in children is as a result of laryngotracheal stenosis, supraglottic stenosis, and laryngomalacia. Laryngotracheal stenosis, which develops at the posterior commissure and the subglottic area and can cause typical relapsing paroxysmal laryngospasm, is mostly nocturnal and typical of children. Supraglottic stenosis is typical of the neonatal period and due to reflux in a large proportion of cases, and in most cases there is vestibular involvement. Laryngomalacia also typically presents in the neonatal period and is due to GER in 50 % of cases. This condition is characterized by prolapse of the supraglottic tissue into the glottal space. Symptoms are classically worse during crying and when in prone compared to supine position.

Kaufman [18] produced evidence of a significant link between reflux and laryngeal stenosis: 72 % of children had anomalous pH, monitored over 24 h. GER was presumed to trigger episodes of apnea by acid stimulation of laryngeal, pharyngeal, and esophageal chemoreceptors, causing laryngospasm. However, since these episodes did not show a clear temporal relation with GER, a clear cause-effect relationship could not be

demonstrated [19]. Although the incidence of GER in children with subglottal stenosis is three times greater than in the normal pediatric population, there is no direct evidence that reflux causes or favors subglottic stenosis. Nor is it clear whether GER is caused by increased respiratory effort or whether it plays a role in causing it.

Laryngitis may also be due to GER. The posterior larynx is the most affected area. Hyperemia of the mucosa of the posterior commissure may be a normal or nonspecific finding. Mucosal edema seems to be a more direct expression of a cause-effect relationship with reflux. The laryngeal damage that occurs in LPR is not caused by acid alone, but it requires both acid and activated pepsin, and it must be remembered that pepsin remains active even at a pH of 5.4 [20]. When compared to the esophageal mucosa, the laryngeal mucosa is injured with much lower levels of acid/pepsin exposure. It has been accepted that the extrinsic defense mechanisms between the laryngopharynx and the esophagus are markedly different, with the latter having much more resistance to acid peptic exposure. In fact, the intrinsic defense mechanisms of the laryngeal and esophageal mucosa are also different. One of the carbonic anhydrase (CA) isoenzymes, CA III, has been shown to have increased expression in the esophageal mucosa in response to refluxate exposure, whereas the larynx demonstrates a depletion of CA III after chronic reflux exposure. Furthermore, although esophageal mucosal response to acid/pepsin exposure appears to often be readily reversible, laryngeal mucosa can easily be damaged irreversibly [21, 22].

Respiratory Manifestations of Extraesophageal Reflux

The association between GERD and a number of pulmonary diseases including recurrent pneumonia, asthma, bronchitis, bronchopulmonary dysplasia, and cystic fibrosis is well described. In children, growth retardation, esophagitis, and subsequent stricture formation, as well as dysmotility and apnea are recognized complications of aspiration.

Perhaps the strongest association appears to be with "non-asthma" wheeze. Most patients with asthma may also have coexisting GERD. The most common reason for improvement of refractory asthma may be appropriate treatment of GERD. However the cause and effect relationship between asthma and GERD is difficult to establish since either condition may induce the other. An asthmatic attack can cause esophageal reflux of gastric contents by creating a negative intrathoracic pressure that overcomes the LES barrier. Alternatively GERD, either by direct microaspiration mechanism or indirectly by stimulating the distal esophageal sensory vagal nerve, may induce bronchospasm and asthma. Additionally, asthma may produce GERD by having an adverse effect on esophageal physiology by some of the medications used for the treatment of asthma. i, beta2-agonists, and even prednisolone may increase esophageal exposure to acid reflux by affecting the protective mechanisms of reflux.

Limitations of Current Diagnostics for Extraesophageal Reflux

Ambulatory 24-h double-probe (esophageal and pharyngeal) pH monitoring [23] is being overtaken as the gold standard for diagnosing EER, as proximal pH testing has been shown to be lacking in reproducibility. Vaezi et al. [24] demonstrated reproducibility of proximal pH testing as low as 55 % for patients with proximal esophageal acid reflux. Indeed, the outcome of pH testing may also be dependent upon the position of the proximal sensor relative to the upper esophageal sphincter (UES). Use of fixed-spacing catheters placed with reference to the lower esophageal sphincter (LES) results in variable placement of the proximal probe relative to the UES. In a study of 661 patients, McCollough et al. [25] (using a dual-channel esophageal pH sensor with fixed 15-cm spacing pH catheter) observed the proximal pH sensor in the hypopharynx, UES, or proximal esophagus in 9 %, 36 %, and 55 % of patients, respectively, and found that proximal

probe placement within or above the UES substantially reduced the correlation between proximal and distal sensors. In a meta-analysis of studies of proximal pH probe measurements in normal subjects and patients with LPR, Meyer et al. [26] demonstrated that variability in placement of the proximal probe may have a profound impact on our ability to determine an association between proximal reflux and extraesophageal symptoms. Moreover, McCollough et al. [25] noted a significant correlation between the extraesophageal symptoms and proximal esophageal reflux when the UES rather than the LES was used as a reference to place the proximal sensor. All studies that had failed to show such an association had employed a fixed-spacing catheter referenced to the LES.

It is now well recognized that pH monitoring is incapable of detecting nonacidic gastric reflux, which has been shown to be a contributing factor in airway disease. Much of the evidence demonstrating the association between nonacidic reflux and airway disease has been determined by combined multichannel intraluminal impedance (MII) and pH monitoring. This technique offers several advantages over pH monitoring, including differentiation between direction of flow (antegrade and retrograde) of bolus movements, characterization of refluxate constitution (gas, liquid, or solid), the capacity to measure sequential reflux events occurring while intraesophageal pH is less than 4.0, and detection of nonacidic reflux. However, briefly, Wenzl et al. [27] found nonacid rather than acid reflux symptom correlation in 77.6 % of infants with reflux-associated apnea. Tutuian et al. [28] demonstrated that cough was associated with nonacid reflux in 26 % of 50 patients with persistent cough refractory to treatment with proton pump inhibitors (PPIs). The combination of pH/MII and high-resolution manometry has more recently been utilized to assess laryngopharyngeal reflux in more detail and appears to be promising, but is observer dependant and is only available at specialist centers. Although combined MII-pH monitoring has significantly enhanced our ability to detect and characterize reflux, it continues to be expensive, is invasive, and has limited availability. In certain instances, a simpler and less invasive technique amenable to serial testing may be preferred.

Pepsin/Pepsinogen as a Marker of Extraesophageal Reflux

Pepsin is a digestive protease, released by the chief cells in the stomach. It derives from pepsinogen, which is the storage form in the gastric chief cells. When stimulated by gastrin and the vagus nerve, the chief cells and the parietal cells release pepsinogen and HCI, respectively. The acidic pH created by HCI allows pepsinogen to undergo an autocatalytic cleavage into the active enzyme, pepsin [20]. This acid environment is necessary for the enzymatic activity of pepsin, which is inactivated at a higher pH. Although the constitution of gastric refluxate is variable and components, such as acid or bile salts, may or may not be present, all refluxate contains pepsin, but not all reflux occurs below pH 4.0 [29, 30]. Thus, with use of traditional gastroenterology standards for pH-metry, significant LPR may be underdiagnosed. Indeed, pepsin exhibits enzymatic activity at pH levels well above 4, and it is only irreversibly inactivated at a pH greater than 6.5. Thus, a patient could conceivably have a negative pH study (no reflux events pH <4) but might still have significant LPR-related disease. It has been reported that the laryngeal epithelium is far more sensitive to damage by pepsin in the presence of acid than is esophageal epithelium and that may help explain why the patterns of reflux, reflux mechanisms, and clinical manifestations of LPR and GERD are so different [20].

Pepsin assay has the capacity to detect nonacidic reflux and may be used to monitor reflux in patients undergoing treatment with PPIs. Superior to pH and MII testing, pepsin analysis may be performed on samples as easily obtainable as saliva and sputum, thereby facilitating testing. This is particularly relevant in children and the neurologically impaired individuals in whom the more invasive diagnostic investigations are often associated with technical difficulties and in many cases not

tolerated. Pepsin assay also offers the advantage of direct detection of refluxate at sites of airway damage potentially attributable to EER. Although pepsin assay alone does not indicate a causal relationship to airway damage, the presence of pepsin in the airway does indicate reflux. To date, this technique has demonstrated the presence of pepsin in the trachea, lung, sinus, middle ear, combined sputum and saliva, and exhaled breath condensate [31–35]. Currently used methods rely on one of two means for the identification of pepsin in the airways: enzymatic or immunologic.

Enzymatically active, rather than inactive, pepsin is predicted to be most physiologically relevant to disease. Detection of peptic activity typically entails exposure of a sample to acidified substrate and quantification of substrate digestion by protein precipitation and spectroscopy or other methods. The pepsin concentration in the sample is determined by comparing enzymatic activity to that of standard and normalized to total sample protein to allow comparison between samples. Whereas the pepsin precursor, pepsinogen, is only known to be synthesized in the gastric fundus, isozymogens of pepsinogen have been identified in other tissues of the body, and pepsinogen is frequently observed in serum, albeit at lower levels, particularly in patients with gastritis [36]. Pepsinogen in patient samples would be converted to active pepsin upon addition of acidified substrate during the assay, thereby potentially leading to false positives. Thus, appropriate controls, such as detection of pepsinogen messenger RNA in surrounding tissue [37] and comparison of sample pepsin activity [38] should be undertaken to prevent assay interference by local pepsin synthesis and contamination by serum pepsinogen. Because the enzymatic method of pepsin detection is a measure of protein digestion, interference by other proteases must also be considered. Many proteases, such as lysosomal acid hydrolase (cathepsin D), are inactivated by the pH of the assay alone. Assay specificity has been previously documented by abrogating enzymatic activity with the aspartyl protease inhibitor pepstatin or by demonstrating the absence of protease activity in samples obtained from control subjects.

The sensitivity and specificity of pepsin ELISA depend largely on the affinity and specificity of the antibodies employed. To date, relatively few pepsin antibodies have been developed, and many of those currently described are cross-reactive with pepsinogen. Therefore, as with enzymatic pepsin detection, pepsin levels observed in samples must be compared with those of serum to account for contamination with serum pepsinogen. Cross-reactivity with proteins other than pepsinogen has also been reported. In a study to confirm the viability of pepsin as a marker of otitis media, He et al. [39] made an unpublished observation of cross-reactivity of another antibody previously identified in middle ear pepsin to an unknown serum protein questioning the specificity for use in ELISA. However, there has been subsequent development of more specific and better characterized pepsin antibodies. Knight et al. [34] designed an antibody to a region identified by X-ray crystallography to be exposed on the surface of native pepsin, thereby reducing antibody cross-reactivity to pepsinogen to less than 0.03 %. Cross-reactivity to other sample proteins has been further characterized by sodium dodecyl sulfate polyacrylamide gel electrophoresis and mass spectrometry [33]. The antibody used in combination with a polyclonal hum pepsin 3b antibody generated an ELISA that was 100 % sensitive and 89 % specific (according to pH-metry) for diagnosing reflux from the sputum of patients with suspected LPR.

The specificity of immunologic detection may also be improved through the use of alternative techniques such as Western blot analysis. Using the antibody designed by Knight et al. [34], Crapko et al. [33] performed Western blot analysis to demonstrate the presence of pepsin in middle ear effusions of pediatric patients with otitis media. Kim et al. [20] found Western blot analysis of combined sputum and saliva to have a sensitivity and specificity of 89 % and 68 %, respectively (according to pH-metry), for diagnosis of EER and used the assay to demonstrate an increased incidence of sputum pepsin during reflux symptoms relative to rising or before sleep.

Pepsin assay has been used to identify refluxate in the trachea, lung, sinus, middle ear,

combined sputum and saliva, and breath condensate. An immunological pepsin assay of combined sputum and saliva was determined to be 100 % sensitive and 89 %[40] specific for detection of EER (based on pH-metry) and an enzymatic test of nasal lavage fluid (100 % sensitivity and 92.5 % specificity) [41].

O'Reilly et al. determined that pepsin was detectable in the middle ear cleft of 20 % of pediatric patients with OM undergoing tympanostomy tube placement, compared with 1.4 % of controls. Recovery of pepsin in the middle ear space of pediatric patients with OM was found to be an independent risk factor for OM. Patients under 1 year of age were found to have a higher incidence of purulent effusions and pepsin-positive effusions [42].

Tasker et al. [43] using enzyme-linked immunosorbent assay (ELISA) to analyze middle ears secretions, obtained by tympanocentesis, in 54 children with middle ear infection, found concentrations of pepsin and pepsinogen, about three times the magnitude greater than in serum. Albumin concentrations were the same, indicating that the origin of pepsin, in the middle ear secretions were GER and not transudation. However, an epidemiological review of an international literature did not bring any differences to light in the incidence of middle ear infection between newborns and children with a history of GER and controls. There could be even a "protective" relationship between the two. In other words, GER may be associated with a major confounding factor in reducing the incidence of middle ear infection: during diagnostic screening, children with GER may be assessed and treated for allergy resulting in a lower frequency of otitis media.

A prospective study investigating the relationship between GER and chronic otitis media effusion (OME) confirmed the presence of gastric enzyme in the middle ear effusion (MEE) of children with OME. Samples were taken at the time of tympanostomy tube placement and total pepsinogen concentrations of effusions and serum samples were measured with a commercial ELISA using human pepsinogen I specific antibody. Measurable pepsinogen was present in all MEEs from patients, with levels higher than the serum values. The difference between the levels of pepsinogen measured in MEE and serum was statistically significant ($p<0.01$), but albumin levels were higher in serum than in MEE and the difference was statistically significant ($p<0.01$) [44].

Analysis of pepsin/pepsinogen in middle ear effusions was considered a reliable diagnostic marker for assessment laryngopharyngeal reflux (LPR) in children with otitis media with effusion (OME) in another small cohort of 31 patients. Ambulatory 24-h dual-probe pH monitoring was carried out on 31 children with OME. Middle ear effusions were collected from 17 children during myringotomy. Total pepsin/pepsinogen concentrations in effusions were measured by ELISA using antipepsin antibody. Dual-probe pH monitoring showed that 22/31 (71 %) of the studied children had significant LPR. The concentrations of pepsin/pepsinogen in middle ear effusions were found to be up to 4.5–231.44 times higher than the serum levels. There was a significant positive correlation between the level of pepsin/pepsinogen assayed in the effusions of the 17 children and the number of pharyngeal reflux episodes measured by pH monitoring [45].

Evaluation of Lung Fluid

Patients with aspiration-induced pulmonary disease are usually evaluated for dysfunctional deglutition with VFSS and contrast studies. Unfortunately, aspiration due to GERD is rarely seen in barium studies. Alternative methods for diagnosis of GER include esophageal manometry and pH probe monitoring. However, these are only indirect indicators of aspiration-induced pulmonary disease. Bronchial scintigraphy in conjunction with a meal offers several advantages in evaluating GERD. Advantages include the physiologic nature of the study, direct visualization of aspiration, a prolonged observation period, and low radiation exposure.

Evidence that GERD is the etiology in the development of chronic cough and bronchospasm has been, for the most part, indirect and

controversial. Coughing and wheezing have improved following medical or surgical treatment of GER. Patients suspected to have pulmonary disease secondary to aspiration are traditionally evaluated for pharyngeal aspiration due to dysfunctional deglutition. Historically, barium studies and FEES have been very reliable in making this diagnosis. However, these are both dynamic studies therefore making it far more difficult to evaluate pulmonary aspiration occurring due to GERD. Traditional methods of analysis for GER including esophageal manometry and pH probe monitoring have been used only as indirect indicators of aspiration-induced pulmonary disease. Indeed, although barium studies for evaluation of GERD have been very successful, actual detection of gastroesophageal aspiration has been disappointing, even in those patients known to have secondary pulmonary disease. Numerous biomarkers in serum, sputum, and bronchoalveolar lavage (BAL) have been studied, and their role in the recognition of aspiration remains controversial at this time.

Lipid-Laden Macrophages in BAL

Lipid-laden alveolar macrophages (LLAM) are macrophages in which ingested lipid can be visualized inside the cells on microscopic examination and are a well-recognized biomarker for aspiration. The presence of LLAMs in the BAL fluid has long been considered as a marker of lipid aspiration. Corwin and Irwin examined the validity of LLAMs as a marker of aspiration in the BAL of patients with various parenchymal lung diseases in 1985. Semiquantitative determination of LLAM index was calculated in 49 patients with parenchymal lung diseases (9 of them were aspirators and 40 nonaspirators). Macrophages were graded by the amount of lipid in the cytoplasm of each macrophage with a score of 0–4. A total of 100 macrophages were evaluated with a score ranging from 0 to 400. The LLAM index was increased in the lung disease group compared with controls. Moreover, LLAM indices were higher in the aspiration group than in nonaspirators. A LLAM index of 100 or greater was associated with a sensitivity and specificity of 100 % and 57 %, respectively. Accordingly, the authors suggested that LLAM index could be a helpful tool in excluding aspiration as a cause of parenchymal lung disease [46].

There are numerous studies in adults and children that have subsequently reported on LLAM as marker of gastric aspiration [47–50]. Furthermore, the association between aspiration and LLAMs has been more objectively elicited using the standard diagnostic tools to confirm the suspicion of GER-related aspiration. In one cohort of 20 children with refractory respiratory symptoms, LLAMs in BAL were higher in patients who had confirmed GER on pH monitoring, compared with those who had negative pH-metry [51]. Similarly the "lipid index" (reflecting the amount of lipid in 100 consecutive macrophages) was higher in the induced sputum of adults with gastric content aspiration (defined as a fall of pH <4 at the upper esophageal electrode on 24-h pH recording), compared with those without aspiration. No clinical symptoms of aspiration and normal chest radiographs were reported in the 33 patients enrolled in that study [52]. These results have been corroborated in children with chronic chest disease and GER compared with children with recurrent pneumonia without GER [53]. Nussbaum et al. compared a group of 74 children with chronic respiratory disease and documented GER to a group of 41 children with chronic respiratory disease without GER. LLAM were found in 85 % of the GER group and 19 % of the non-GER group ($p < 0.0001$). Published cutoff values for LLAMs, however, vary significantly from 65 to 200 [50, 54, 55]. There has also been significant overlap of LLAM indices between patient groups with underlying lung disease. Moreover, considerable overlap of LLAM indices was observed between healthy children and those with pulmonary diseases. For instance, LLAM indices in children without chronic lung disease were higher than those reported for healthy adults [46]. It has therefore now been recommended that each institution must determine its own LLAM index cutoff value [56]. Only higher values yielded acceptable sensitivity and specificity for aspiration in children [57].

Recent studies did not show a significant correlation between LLAMs and aspiration. In a murine model, detection of starch granules in BAL was superior to LLAM index; the latter had a low specificity, while the presence of starch granules in the BAL yielded 100 % sensitivity and specificity for aspiration. The LLAM index was not different in mice that had starch aspiration versus those who had *Pseudomonas aeruginosa* administered in their airways [58]. These conclusions were corroborated in human studies. While examining the correlation of LLAMs with the diagnosis of chronic pulmonary aspiration in children, Bauer and coworkers [59] found a significant overlap in the LLAM values between the aspirators and the nonaspirators group, which led the author to conclude that the LLAM index cannot stand alone as a gold standard for the diagnosis of chronic pulmonary aspiration. Furthermore, LLAM indices were found to be elevated in children with pulmonary diseases without clinical evidence of aspiration and were similar to indices previously reported in children with pulmonary aspiration. The lack of specificity of LLAMs for aspiration was reiterated when the lipid-laden index was found to be higher in children with chronic respiratory symptoms, particularly in those with cystic fibrosis, and had no correlation with the presence or absence of GER determined by intraesophageal pH monitor [50]. Other studies confirmed the lack of correlation between GER and LLAM indices, in the presence of respiratory symptoms [60] and in those without lung diseases [61], even when the diagnosis of GER was based on pH monitoring and endoscopy [62]. These observations suggest that increased LLAM index can be found in a variety of pulmonary disorders and is not likely to be specific for silent aspiration. In fact, the LLAM index might be affected by other factors, regardless of the presence or absence of aspiration, as was illustrated in neonates receiving intravenous lipid infusion who had higher LLAM indices than those who were not [63]. An elevated LLAM index has also been reported in cases of pulmonary fat embolism, sickle cell anemia, acute chest syndrome, cancer, graft-vs-host disease, and inhalation of organic dusts [64–66].

Lipid-laden alveolar macrophages by themselves seem to lack specificity for diagnosing aspiration, even when they are assessed using quantitative methods. Their role in diagnosing aspiration and guiding its treatment is very limited at this time. Assessment of the LLAM accuracy rests on its relationship to some way of knowing whether chronic pulmonary aspiration is truly present or not. Unfortunately, a gold standard for accuracy for the diagnosis of chronic pulmonary aspiration does not exist.

Pepsin in BAL

The absence of pepsin from the pulmonary and bronchial tissues makes its presence in lung aspirates an indicator of gastric content aspiration. There are a number of investigations that have examined the role of pepsin as a biomarker for aspiration both in humans and in animal models. Using a pepsin assay developed by Anson [67], Badellino et al. tested the above hypothesis in a rabbit model [68]. Human gastric juice (2 ml/kg) was instilled intratracheally into 24 rabbits; similar volumes of isotonic sodium chloride solution were instilled intratracheally in control animals. Bronchiolar lavage (BAL) was performed 15, 30, or 60 min after the instillation of fluid. In the rabbits given human gastric juice, peptic activity was detected in the lavage fluid in eight out of eight animals at 15 min, six out of eight at 30 min, and five out of eight at 60 min. Because the Anson method relies on the presence of proteolytically active pepsin to digest a hemoglobin substrate, it cannot be used to detect pepsin that has been degraded in the alkaline environment of the lung. This factor explains why fewer specimens tested positive for pepsin at the 30- and 60-min times. No peptic activity was present in lavage fluid from control animals at any time. Similar findings were elicited in another experimental investigation where pepsin was detected in the tracheal aspirates of rabbits that were exposed to single or multiple gastric juice aspirations, but not in the control group [69].

Detection of pepsin in tracheal aspiration samples has been proposed as a reliable marker

of gastric contents and microaspiration in children. Using an immunoassay with rooster polyclonal antibodies to purified human pepsin, the role of pepsin as a marker of gastroesophageal reflux (GER)-related pulmonary aspiration was studied in 56 children undergoing anesthesia as part of the workup for GER. The study group was compared with positive controls, who had proven aspiration (milk suctioned from endotracheal tube), and with 13 negative controls without GER or respiratory symptoms. The positive control group had significantly higher BAL pepsin levels compared with the negative controls. However, only patients with proximal GER on pH-metry (but not distal GER) had significantly increased pepsin in BAL. Surprisingly, in children with combined distal and proximal GER, only those who complained of chronic cough had significantly increased pepsin levels [70]. Similarly, 64 children who underwent endoscopy for clinically significant GER were compared with a control group of 34 children scheduled for routine surgeries [38]. The two groups were subdivided based on the presence or absence of associated respiratory symptoms. Pepsin was detected in tracheal aspirates in seven out of eight children with history of chronic respiratory symptoms and in 31 out of the 37 children with both reflux and chronic respiratory symptoms. It was also observed in 7 out of 27 patients who had only reflux symptoms. By contrast, none of the 26 children who had neither reflux nor respiratory symptoms had pepsin in their tracheal aspirates. Overall, children with pepsin-positive tracheal aspirates were more likely to have a clinical diagnosis of GER than the pepsin-negative group [71].

In premature neonates, chronic gastric aspiration is thought to contribute to the development of bronchopulmonary dysplasia. Farhath and colleagues relied on measuring pepsin in the tracheal aspirates on neonates on ventilator support by detecting aspiration due to GER [72]. Serial tracheal aspirates obtained from 45 premature neonates revealed the presence of pepsin in 92 % of the samples suggesting significant aspiration of gastric contents. In those neonates, enteral feeding was associated with a higher level of pepsin compared with unfed infants. Camacho and colleagues extended these observations by reporting the presence of pepsin in 91.4 % of tracheal aspirates of 59 premature neonates of whom 31 developed bronchopulmonary dysplasia [31]. Enzymatic assays in these studies measured both pepsin and pepsinogen because secretion of pepsin is inconsistent and low in infants, and measuring only pepsin in tracheal aspirate samples could have underestimated the prevalence of aspiration in premature infants [73].

There are a number of limitations that are worth mentioning regarding the use of pepsin. First, most of the human studies assumed the validity of pepsin as a marker for aspiration and did not compare it to a gold standard test. However, the relatively consistent results in animal models and human investigations suggest that pepsin might be a useful marker of aspiration, especially in patients who also have aspiration-related pulmonary diseases. Second, because pepsin activity can only be detected in the BAL for a short period of time following aspiration, only events that occur in a controlled environment where specimens can be rapidly collected (i.e., ICU) are likely to be detected. Third, a significant drawback of using molecular markers of aspiration in BAL samples is the inability to standardize the concentration. It is not known how BAL pepsin concentrations change over time following an aspiration event. Elevated levels may reflect less dilution at the time of sampling, high volume and/or high frequency aspiration events, or impaired clearance by the lung itself. Advanced molecular diagnostic techniques are currently under development for using undiluted BAL samples in detecting pepsin.

Soluble Triggering Receptor Expressed on Myeloid Cell 1

The triggering receptor expressed on myeloid cells (TREM) is a family of receptors expressed on polymorphonuclear neutrophils and mature monocytes, characterized by the presence of a single immunoglobulin-like domain. It has been shown that there is an upregulation in the

expression of TREM-1 after TLR activation, and soluble TREM-1 (sTREM-1) was initially thought to be a more specific marker for infection, when measured in body fluids [74–77]. However, other studies questioned the specificity of sTREM-1 for infectious processes. sTREM-1 has been shown to be increased in noninfectious disorders, such as systemic inflammatory response after multiple trauma [78] and inflammatory bowel disease [79], as well as in the synovial fluid of patients with rheumatoid arthritis [80].

The diagnostic utility of sTREM-1 in aspiration syndromes is limited by the scant investigations that are available. One study measured both blood and alveolar levels of sTREM-1 in order to differentiate between bacterial aspiration pneumonia and gastric aspiration pneumonia. A total of 75 patients who had a witnessed aspiration event and 13 controls without underlying pulmonary disease underwent BAL and microbiological analysis of respiratory sections. While plasma sTREM-1 levels were comparable between the controls and those with aspiration syndromes, the alveolar sTREM-1 levels were higher in the aspiration group with culture-positive BAL compared with those with culture-negative BAL. A BAL sTREM-1 cutoff value of 250 pg/ml was 65.8 % sensitive and 91.9 % specific for bacterial aspiration pneumonia [81]. Although promising, the usefulness of measuring sTREM-1 in clinical practice has to be determined prospectively in dedicated studies.

Aspiration syndrome is a frequent problem, which particularly affects a vulnerable population and is often missed or misdiagnosed. When patients are medically evaluated after an aspiration event, it is usually for one of many possible diagnoses or pathophysiologic processes. Patients could be presenting with a reversible noninfectious aspiration-induced chemical pneumonitis, an aspiration-related bacterial pneumonia, or with ARDS. However, the classic assumption that gastric content is sterile and that bacterial pneumonia after gastric aspiration is usually a secondary superinfection following acid-induced lung injury may not be entirely true. Aspiration of nonacidified gastric contents could clearly pick up viable endogenous flora when regurgitated into the oral pharynx before entering the trachea. Additionally, the widespread use of acid suppressive therapy, especially in the population at risk for aspiration, might change the gastric pH allowing for its colonization with bacteria [82]. Furthermore, when food particles are aspirated, it is difficult to assume that they are completely sterile, even when they are aspirated after staying in the stomach for a short duration.

Finding a way to differentiate between the distinct types of aspiration could have significant prognostic and therapeutic implications. Unfortunately, the basic pathophysiologic principles of aspiration syndromes have yet to be materialized into validated clinical tools that would provide distinct “signatures” of aspiration pneumonitis versus bacterial aspiration pneumonia. Alternatively, analysis of cytokine combinations using a multiplex microarray ELISA technique has shown promise in animal models but its relevance in clinical decision-making awaits validation in human trials. Exhaled breath condensate may provide a simple approach to biological samplings but its reproducibility remains under scrutiny. The most crucial question, however, is how to overcome the problem of a lack of a reference for the diagnosis of aspiration. Until an accurate and valid gold standard is established, the appropriate strategy is to gain additional information using different clinical and molecular techniques. The real advantage of biomarkers as an index of infection would be to unveil unrecognized facets of the clinical problem, thereby increasing the validity of clinical estimates.

Summary

In otolaryngologic practice, recognition of many of the clinical manifestations of EER has gained acceptance [1–3]; however, the prevalence of otolaryngologic and respiratory disorders caused by EER remains unknown. In part, this appears to be because currently used diagnostics for EER often rely on testing methods and normative standards that were established for the diagnosis of classic gastroesophageal reflux disease (GERD),

which may not be appropriate for use in diagnosing EER disease.

The current clinical practice of treating children with extraesophageal symptoms for GER is increasing, but there is little data to support it. There is still a lack of accurate means for diagnosing GER; 24-h pH monitoring with double/triple probes (distal and proximal esophageal and/or nasopharyngeal probe) is the "gold standard" for diagnosing ENT manifestations. Recent advances with high resolution offer more promise in particular when used together with videofluoroscopy and pH/MII.

The tools and standards of diagnosis developed for GER lack the sensitivity to detect less frequent and more weakly acidic proximal reflux, which has been associated with upper airway disease. Pepsin has been proven to be the most sensitive and specific marker of EER of any gastric component tested to date. Pepsin assay permits direct detection of reflux in regions of the airway that are beyond the reach of pH and MII monitoring and offers an inexpensive, noninvasive method for the detection of EER. The assay has proven effective in diagnosis of EER from fluids as easily obtainable as combined saliva and sputum, and its simplicity lends itself to the development of platforms for in-clinical testing. Continued characterization of the presence of pepsin in the airways is certain to reveal patterns indicative of airway disease and severity and provide insight into the contribution of pepsin to EER-associated disease.

Aspiration has been shown to be responsible for both acute and chronic respiratory disease. Though pharyngeal aspiration is more easily and frequently detected, GERD aspiration provides an important underlying cause of respiratory disease. Diagnosis of GERD is therefore essential for the treatment of pulmonary disorders. Although multiple diagnostic options exist, only nuclear scintigraphic and barium studies offer direct evidence of aspiration. Unfortunately, at this time none of the available markers provide an accurate tool for guiding the diagnosis and the management of aspiration. Systemic biology approaches in which microarray data are enriched with high-throughput comparative genomic and proteomic analysis may hold the key to future studies in aspiration syndromes.

Continued characterization of the presence of gastric refluxate in the airways and ENT system is certain to reveal patterns indicative of EER disease and severity and provide insight into the contribution of fluid evaluation to EER-associated disease.

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Part XIV

Treatment Approaches for GERD: Lifestyle Changes

Feeding Changes and Positioning Therapy for Infants

83

Ahmed Sarkhy and Mike Thomson

Feeding Changes

One of the initial conservative interventions that has been tried for a long time for treatment of gastroesophageal reflux (GER) is to modify the infant feeding by different measures such as feeding babies with small volume, but frequent feeds, or changing the formula composition by adding thickening agents. Several studies tried to evaluate the efficacy of these interventions which had some controversial results. Below is a summary of the available current evidence around these interventions:

Small Volume, Frequent Feeding

One of the commonest reasons for regurgitation is overfeeding. Small volume but frequent feeding technique has been tried to overcome this problem aiming to reduce the amount of gastric contents and therefore reducing the GER events. However, this technique was found to be a time-consuming for the parents and may not satisfy the hunger of a crying baby for more feed. Furthermore, there is a concern that significant volume reduction may deprive the infant from the required calories to grow, and this is even worse in infants who suffer from poor weight gain because of significant GER symptoms. Therefore, this technique was found to be impractical and difficult to apply [1]. Volume reduction is only needed in overfed babies who are thriving well.

Low-Fat, High-Carbohydrate Feed

At one point, a low-fat, high-carbohydrate feed was suggested in GER management in infants hoping to reduce reflux events through avoiding delayed gastric emptying associated with fat content. This technique was found to be ineffective and even associated with higher rate of GER events [2]; therefore, it is not any more recommended in the treatment of GER/GERD.

Hydrolyzed Protein Formula

Because some symptoms of milk protein allergy can overlap with those of GERD in infants, some physicians tend to change the milk protein source particularly if there is a suspicion of allergy. The most recent combined North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) clinical practice guidelines suggest that formula-fed infants with recurrent

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vomiting may benefit from a 2- to 4-week trial of an extensively hydrolyzed protein formula [3].

Thickening of the Feeding Formula

Thickening of the feeding formula is a common intervention that is used as a first-line treatment for GER. Different agents have been used to thicken the formula including cereal, rice, carobbean gum, pectin, and cellulose. A thickened formula thought to be retained more in the stomach and therefore tend to reflux less into the esophagus.

The effect of the thickened formula on GER symptoms gets the attention of clinical research for many years. It was found to be associated with less regurgitation events, less crying times, and more sleeping hours in observational studies [4–6]. Several experimental quasi or controlled trials were conducted to evaluate the efficacy of thickened feeds for the treatment of GER in healthy infants [7–15]. In general, these studies agreed on the point that thickened formula found to be helpful in reducing regurgitation events; however, it does not have any effect on the reflux index; no significant adverse events were reported in these trials.

Several systematic reviews were also conducted over the past few years to evaluate the efficacy and safety of this intervention [16–19]. The most recent systematic review with meta-analysis was conducted by Horvath et al. which included 14 RCTs with either a parallel or crossover design. These RCTs included infants who were diagnosed with GER or excessive regurgitation and/or vomiting, but otherwise healthy. The included RCTs evaluated different types of thickening agents that were used with variable durations (1–8 weeks) and compared to the standard non-thickened milk formula. The methodological quality varied significantly among the included studies. The meta-analysis demonstrated that compared to standard formula, "the use of thickened formulas significantly increased the percentage of infants with no regurgitation, slightly reduced the number of episodes of regurgitation and vomiting per day, and increased weight gain per day." The meta-analysis did not find any effect of the thickened formula on the reflux index, the number of acid GER episodes per hour, or the number of reflux episodes lasting >5 min. This review did not find any significant adverse events, and there was no difference between the different types of thickening agents used in those trials [19]. Though there was a significant heterogeneity between the included studies, the findings from this meta-analysis are consistent with the findings from the previously reported systematic reviews [16, 18] that showed a modest effect of the thickened formula feedings in reducing GER events, but not the reflux index. The recent combined NASPGHAN and ESPGHAN clinical practice guidelines of GERD diagnosis and management had the same conclusion [3]; however, as stated in these guidelines, further studies are still needed to study the impact of thickened formula on the natural history of physiologic GER or GERD [3].

Are Thickened Formulas Risk-Free?

Earlier reports raised some concerns about using the thickening agents in infants feeding. Some of these concerns included a potential problem of an excessive energy intake and changing the nutritional components of the feed particularly with the homemade thickened feeds [20]. Another concern was raised about a potential risk of allergy from the added thickening agents [21]. In addition, studies in vitro models demonstrated that thickening agents may affect the absorption of some micronutrients particularly when the indigestible carbohydrates used as thickeners [22]; however, this was not reported in human studies. And finally, one study found an increase risk of coughing in infants given thickened formula [23].

It is important to recognize that some of these adverse events were reported at the time of early use of these thickening agents. Using currently available pre-thickened formulas or what is called anti-regurgitation formulas (AR formulas) which designed to have a similar osmolarity of the stan-

dard formula with no extra caloric density and with a proper nutrient profile eliminate the risk of slow feed flow through the standard nipple holes, excessive energy intake, or changing the nutritional components of the feed; however, parents who are interested to prepare thickened formula at home should be taught how to do it well by their physicians to avoid these risks [13, 20]. Nearly all of the published RCTs did not find significant adverse events when thickened formula used; however, this can be just related to the fact that the RCTs were not designed to evaluate the adverse events which usually need a longer duration of follow-up or a larger number of patients for an adverse event to be detected. In general, we believe that the currently available commercial pre-thickened formulas are safe to be used as a therapeutic trial in infants with uncomplicated GER symptoms.

Position Changes for GERD Management

Finding an optimal body position to treat gastroesophageal reflux (GER) has generated much interest over a number of years. Since infants are lying flat most of the time, they are more prone for regurgitation of the gastric contents postprandially. This led to the introduction of the postural treatment as a therapeutic measure for gastroesophageal reflux, presuming to promote gastric emptying and therefore to reduce GER events, without the need for potentially unnecessary pharmacological interventions. The proposed effect of position change was presumed to be likely to be related to the anatomical configuration of the stomach and gastroesophageal junction [24].

Several studies demonstrated that positioning infants prone or in the left lateral position after feeding reduce the frequency and duration of GER events compared to supine position or right lateral position [24–28]. However, because of the associated risk of the prone position with sudden infant death syndrome (SIDS), it is not any more recommended in GER management. The left lateral position is quite difficult to implement and maintain, and in addition, it is an unstable position for an infant who may fall into the prone position and have a risk of SIDS. Therefore the current clinical practice guidelines from NASPGHAN and the ESPGHAN do not recommend the prone or side-lying position to treat reflux in infants, and, therefore, the supine position during sleep is the least harmful position that infants may sleep at [3].

The question then comes: does head elevation position reduce GER? To answer this question, several studies were conducted. One of the earliest RCTs was conducted by Orenstein SR et al. In this study, nine infants with documented GER participated in a trial with crossover design where infants observed in an infant seat (inclined at 60°) and then in the horizontal prone position for 2 h after feeding. Interestingly, the authors found that positioning infants in an infant seat actually increase reflux compared with the prone position [29]. In another study, the same author tried to determine whether head-elevated prone positioning (at 30°) is better than flat prone positioning in 100 infants with GER using esophageal pH monitoring. The study showed no significant difference in the reflux index between the flat and head-elevated prone positions [30]. Carroll et al. conducted a systematic review to evaluate nonpharmacological therapies for GERD such as position changes in infants. Only two RCTs met the inclusion criteria of this review, both of them utilized esophageal pH monitoring as their outcome measure. The authors concluded that neither the upright position nor using the infant seat reduce the amount of reflux [16]. A Cochrane review published in 2004 looked to the effect of elevating the head of the crib on GER management; five RCT studies with crossover design were included in this review, and all of them used esophageal pH monitoring. Each of these studies looked to the effect of different positions, making it difficult for the reviewers to compare them head to head and based on the interpretation of the individual data. Their final conclusion was that elevating the head of the crib in the supine position does not have any effect on GER [18]. A number of devices such as the anti-regurgitation bed (AR

bed) have been employed and are yet to be properly researched.

In conclusion, the clinical effectiveness of position changes in GER treatment in infants is controversial. The current evidence discourages using the prone position in infants with GER and, in addition, does not recommend the side-lying position of the infants to treat gastroesophageal reflux.

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Lifestyle Changes in Children and Adolescents

84

Donald J.S. Cameron

Gastroesophageal reflux (GER) in otherwise well, older children and adolescents is different from that in newborns and young infants. It may be a continuation of GER starting in infancy [13, 14, 15] or subsequently develop without any pre-existing or predisposing factors. In this sense, it is more comparable to adult GER. One large community-based study reported symptoms of GER in 3–5 % of adolescents surveyed [40].

Children with physical or neurological handicaps comprise a different group with their own particular predisposing factors and morbidity patterns and are discussed elsewhere.

The main symptoms of GER can be categorized into those relating to vomiting or regurgitation of gastric contents and those relating to acid reflux and its complications such as esophagitis.

Regurgitation and Vomiting

GER in childhood usually does not result in forceful vomiting, which should be investigated to rule out other causes. The more usual symptom is of regurgitation into the pharynx or mouth of gastric content, which may be expelled or re-swallowed. Some children may seem to be largely untroubled by it, but others will find it distressing and embarrassing. Halitosis is often a problem leading to social difficulties. Potential effects of GER on the airways, larynx, ears, and teeth have been discussed elsewhere.

Acid GER may also be associated with "heartburn" or other pain and discomfort, with or without endoscopically demonstrable esophagitis (GERD vs. NERD).

Unless GERD has progressed to the point of stricture formation, dysphagia, odynophagia, and obstructive symptoms are more likely to relate to infection, eosinophilic esophagitis, other causes of esophageal inflammation, and mechanical or motility problems than to GER itself. The investigation and evaluation of GER is dealt with elsewhere in this text.

Lifestyle Changes

Lifestyle and dietary changes are frequently recommended as first-line treatment. Intuitively, changes that might help GER include posture, position, thickening of feeds, modification of the

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nature and timing of feeds, reduction of the intake of biologically active substances (such as caffeine, nicotine and alcohol), and weight loss.

Theoretically, gastric emptying might be helped by gravity, smaller feeds, and reduced fat intake, but evidence is sparse. There are, however, few data to support lifestyle effects in children and adolescents, and most have been extrapolated from studies in infants and adults or have become accepted strategies with little or no evidence.

Position

Studies in infants have demonstrated that the prone position is associated with significantly less GER than supine and that the left lateral position is better than right. However, because of concerns about SIDS, any sleeping position other than supine cannot be recommended for infants. The evidence for additional benefit from elevation of the head of the bed is conflicting [9, 52].

In contrast to infants, there are no data to support specific recommendations in older children and adolescents. It seems logical to assume that head elevation during sleep should help by bringing gravity into play. Elevation of the head of the bed may have a place, along with left lateral positioning, in alleviating nocturnal symptoms. Studies in adults have shown significantly less acid exposure [20, 22, 29, 50], but this has not necessarily been associated with improvement in symptoms or antacid use [47].

Intuitively, the right lateral decubitus position might seem to be better by putting the gastric outlet on the downhill side; but acid GER has in fact been shown to be increased in the right lateral position compared with the left in infants [52] and adults [31, 32, 35, 53]. This might simply reflect the "sump" capacity of the body of the stomach in that position. Similar studies have not been done in older children or adolescents. A systematic review in adults [30] concluded that elevation of the head of the bed seems to be an effective measure to improve the symptoms of GER in some patients with GERD. The NASPGHAN guidelines [54] concluded that it is likely that older children and adolescents, like adults, may benefit from elevation of the head of the bed and left lateral positioning for troublesome nocturnal symptoms. This has to be offset by the discomfort in sleeping in such a position.

Obesity

The increasing prevalence of obesity in all age groups might be expected to lead to more GER. Mechanisms could include overeating, increased intra-abdominal pressure, hiatus hernia, and metabolic effects. Reported studies in adults have shown conflicting evidence for obesity as a cause of GER [2, 3, 42], although more recent reports in adults have shown a correlation between BMI and GER symptoms [7, 8, 11, 38, 39, 41, 44]. Data from studies using manometry and/or pH monitoring are less clear-cut with some supporting an association between morbid obesity and GER [14, 15, 18, 21, 26, 28, 56] and others not [6, 34, 51].

Several studies have shown correlation between obesity and waist circumference and increased gastroesophageal pressure gradients, esophagogastric junction disruption, and hiatus hernia [10, 12, 16, 44, 60; El-Serag 2007].

Comparison between different studies has been limited by variable definitions and study designs and differences between countries. However, in a meta-analysis published in 2006, the authors concluded that there was a positive association between increasing BMI and GER in the United States, but heterogeneous results from studies from Europe with both positive associations and no association [7, 8].

Whether GER can be reduced by weight loss is less clear. A number of studies have reported improvement in reflux symptoms. Other studies, however, have shown benefit in both symptom scores and pH-metry from weight reduction in those obese patients with GER symptoms [19, 30]. In a recent study of 179 obese and overweight patients enrolled in a weight loss program (and therefore highly motivated), 38 %

reported GER symptoms. A significant improvement in symptoms was noted with 5 % weight loss in women and 10 % in men with complete resolution of symptoms in 66 % and improvement in 16 % [49].

Another study, however, failed to show such an association in 20 obese patients randomized to an unrestricted diet or a weight loss program with 10 % weight loss [33].

While weight loss is likely to be an effective intervention, further studies and randomized controlled trials are required [30].

There are few reports in children and adolescents. In an interim analysis of 75 overweight and obese children, 25 % complained of GERD symptoms [48].

Diet

In infants GER is usually physiological and improves by about 18 months of age. There is good evidence for the contribution of dietary food protein intolerance in some infants [23–25, 27, 43]. However, in older children and adolescents, there is no evidence for food allergy as a cause of ongoing GER (as opposed to eosinophilic esophagitis) or to support or refute the use of elimination diets in its management.

Acidic fruits and juices have traditionally been taken as aggravating symptoms of GER. Seventy-two percent of 400 patients in one study reported increased heartburn symptoms with citrus juice [17]. However, symptoms do not necessarily relate to pH or effects on LESP [30]. Similarly, although patients frequently complain of increased symptoms, there have been few studies on the physiological effects of spicy foods.

There are a number of reports on the effect of caffeine and chocolate on various physiological parameters such as LESP and acid exposure times with conflicting results [4, 37, 45, 57, 59]. Although it is frequently assumed, the relationship between GER symptoms and coffee, chocolate, and caffeine-containing cola beverages remains unclear, and there is insufficient evidence to warrant their automatic exclusion. However, it goes without saying that foodstuffs which cause pain or discomfort should be avoided [30, 54].

Fat Content, Meal Size, and Timing

Theoretically, as dietary fat results in slower gastric emptying, it could result in increased intragastric pressure and GER. However, there is conflicting evidence for its effect on LESP, acid exposure or reflux symptoms, and no firm recommendations about the limitation of dietary fat can be made [46]. Similarly, there is no clear evidence to support the routine modification of meal size or timing, but, again, individuals may find symptomatic benefit from such changes.

Alcohol, Smoking, and Chewing Gum

Alcohol may affect esophageal motility, LESP, gastric emptying, TLESRs, and gastric acid secretion [5], but there are conflicting reports of its effect on acid exposure times and symptomatic GER. Similarly, smoking is reported to reduce salivary flow and to affect LESP. There are, however, no studies showing that reduction or cessation of alcohol or tobacco exposure significantly improves esophageal pH or GER symptoms [54]. Smoking is, however, significantly associated with the development of esophageal carcinoma in adults with GERD [55, 58]. There are, of course, many more compelling reasons to discourage adolescents from smoking.

Chewing gum has been shown to improve esophageal clearance and reduce acid exposure by increasing salivation and swallowing [1, 36]. Whether this is of clinical and practical significance is debated, and further studies are required.

Most of the preceding discussion is based on studies in infants and adult. Few studies have been performed in older children and adolescents, but it seems reasonable to assume that many of the principles also apply. In adults, GER is usually a chronic disease. In contrast, in the majority of young children and many adolescents,

the symptoms of GER are temporary and improve with time and maturity.

Summary

There are few studies on lifestyle changes and GER in children and adolescents. Extrapolating from adult and infant studies, it seems reasonable to reduce obesity and elevate the head of the bed in symptomatic patients. No general recommendations can be made about dietary modification, but individuals may well find that there are specific foods and drinks that aggravate symptoms and should be avoided. Alcohol and tobacco exposure are of less relevance in children than adults and the role of each in GER is debatable. There are, however, many other reasons to recommend moderation and abstinence respectively.

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Part XV

Pharmacologic Therapies

Pharmacological Reflux Therapies

85

Anil Darbari, Sona Sehgal, Nidhi Rawal, and Rachel Imhoff

Principles of Pharmacological Therapies

The management of GERD was revolutionized by the introduction of histamine type 2 receptor antagonists (H2RA) in the 1970s and even more so with the introduction of proton pump inhibitors (PPI) in the 1980s, [1, 2]. The pharmacotherapy for GERD has expanded as our understanding of the mechanisms leading to GERD has advanced from the role of acid to include TLESRs (transient lower esophageal sphincter relaxations) [3, 4] and recognition that nonacid reflux can cause symptoms in some patients. The goals for pharmacotherapy for GERD are to control symptoms, promote gastric and esophageal tissue healing, improve health-related quality of life, prevent complications, and minimize the adverse effects.

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Acid Suppressants

Histamine Type 2 Receptor Antagonists (H2RA)

H2RAs are competitive, reversible inhibitors of the histamine type 2 receptor (H2R) in the gastric parietal cells. They have several advantages over antacids, including longer duration of action (4–8 h), greater efficacy, and prophylactic use.

The most common drugs in this class include cimetidine, ranitidine, famotidine, and nizatidine. Multiple randomized controlled trials (RCTs) in adults with cimetidine, ranitidine, and famotidine show that they are superior to placebo in improving symptoms and healing the esophageal mucosa [5]. Studies have shown that the efficacy of H2R agonist (A)s in achieving mucosal healing is much greater in mild esophagitis than in severe esophagitis [6]. Randomized controlled trials of infants and children with erosive esophagitis showed significant improvement in clinical and histopathology scores in the cimetidine as compared to the placebo-treated group. Similar results have been seen for nizatidine as well [7]. H2RAs have relatively short duration of action, a disadvantage when compared with PPIs as well as the development of tolerance, and incomplete inhibition of acid secretion [8].

Proton Pump Inhibitors (PPI)

PPIs are the most potent antisecretory agents, which irreversibly bind to the hydrogen-potassium

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ATPase pump in parietal cells, thereby blocking off the final common pathway in gastric acid secretion. PPIs maintain a higher pH for a longer length of time and inhibit all stages of acid secretion including meal-induced gastric acid secretion which results in improved efficacy.

Studies in adults demonstrate faster and better healing of erosive esophagitis with PPIs than with H2RA [9]. The drugs in this class include omeprazole, esomeprazole, lansoprazole, rabeprazole, and pantoprazole. Omeprazole and esomeprazole are approved for use in pediatric patients in Europe and the United States. Lansoprazole is approved for pediatric patient use only in the United States. None of the PPIs are approved for use in infants to date.

Prokinetics

Prokinetic agents enhance gastrointestinal motility, resulting in better esophageal clearance and faster emptying of the stomach contents. They can also effect transient lower esophageal sphincter relaxation (TLESR) [10]. They tend to improve symptoms of regurgitation and vomiting. These drugs work through a variety of different mechanisms. The prokinetic agents include cisapride, metoclopramide, erythromycin, domperidone, bethanechol, and baclofen. Many have significant side effects and there is scarcity of data on their benefit in children [11]. Therefore, they are used in carefully screened patients where their potential benefit outweighs risks.

Adjuvant Therapies

Adjuvant therapies in the treatment of GERD include antacids and surface agents. These tend to provide immediate relief but are recommended for short-term use only.

Antacids

Antacids provide quick but short-lasting symptom relief from GERD. Their effect lasts 1–2 h. Most antacids have magnesium with either aluminum hydroxide or calcium carbonate. They neutralize gastric acid and protect the esophageal mucosa from exposure to acid in the refluxate. In treating esophagitis, pediatric studies have demonstrated that high-dose antacids can be as effective as H2RAs over a 12-week period [12]. However, they are not recommended for chronic because of concern of toxicity especially with aluminum-containing compounds. They are usually used in older children for symptomatic relief.

Surface Agents

Surface-active agents like sodium alginate and sucralfate form a protective coating over the mucosal lining of the stomach, thereby providing a barrier from gastric acid and pepsin. Sucralfate was shown to be as effective as cimetidine in the treatment of peptic esophagitis [13]. Concern for aluminum toxicity from these agents prohibits its chronic use in pediatrics.

Bismuth Compounds

Bismuth compounds include bismuth subsalicylate (BSS) and colloidal bismuth subcitrate (CBS). Bismuth is converted to insoluble complexes by gastric acid and preferentially deposited over ulcer beds where they combine with exposed protein moieties to form a glycoprotein-bismuth complex, providing a barrier from acid and pepsin. They are particularly useful in the treatment of *Helicobacter pylori*-induced disease as they inhibit urease and phospholipase enzymes produced by the bacteria, which help them survive in the acidic environment of the stomach. They are also useful adjuncts in the eradication of resistant *H. pylori* infection in an adults and children [14]. Higher doses and long-term use are associated with significant risks including neurotoxicity, nephrotoxicity, gingivostomatitis, colitis, and osteoarthropathy [15]. The salicylate moiety of BSS does get absorbed by the body and has the potential for causing Reye's syndrome and significant bleeding in patients with coagulopathy or gastrointestinal ulcers.

Combination Therapy

Often, a combination of various pharmacologic agents is used, such as a combination of H2RA and PPI or an acid suppressant and a prokinetic.

In very severe cases of GERD, a combination of pharmacotherapy with acid suppressants and motility agents along with surgical management could be employed.

Combination therapy involves utilization of pharmacologic agents with the same desired effect- such as a combination of acid suppressants. For example, in patients with nocturnal acid breakthrough (NAB) on PPI therapy, the addition of H2RA has shown to be of significant benefit [16]. In an adult study, 64 % of individuals on twice daily doses of a PPI had NAB. The addition of a nighttime dose of an H2RA to the PPI regimen decreased the acid exposure as measured by impedance and pH probe in all but 17 %.

Combination therapy with an acid suppressant and prokinetic may be beneficial in certain groups of patients. These include patients with nonerosive reflux disease who continue to be symptomatic [17]. Patients with certain underlying diseases that predispose to more severe GERD or exacerbation of other systemic diseases like chronic asthma and cystic fibrosis have benefited from combination therapy. In a pediatric study involving children with nonatopic asthma, the group of children receiving a combination of esomeprazole and metoclopramide had much better control of asthma, as good as the control group of children who had undergone fundoplication, while a second group that received only ranitidine alone had significantly more exacerbations [18].

Combination therapy can also be useful in neurologically impaired patients to improve quality of life and decrease the risk of aspiration if they continue having obvious regurgitation and vomiting [19]. Combination therapy also has a role in GERD made worse by abnormal esophageal motility secondary to repaired tracheoesophageal fistula and gastroparesis.

Step-Up vs. Step-Down Therapy

The initial diagnosis of GERD, in children and adults alike, is often based on clinical symptoms. Treatment is initiated to observe a response to therapy and adjustments are made as needed. The dilemma of optimizing treatment and avoiding aggressive therapy when it is not justified or an ineffective approach in patients with severe symptoms or warning signs often dictate the treatment applied. Cost-effectiveness will also influence the treatment [20].

Step-up therapy is usually preferred for mild GERD. It includes lifestyle changes and use of less potent acid suppressants. H2RA are typically employed instead of PPI. Therapy can be escalated by increasing the dose of the medicine or switching to more potent agents as indicated by clinical progression or further evaluation. It could also result in employing combination therapy with acid suppressors and prokinetics. The benefits of this approach are initial low cost of therapy, avoiding unnecessary medication, and decreased side effects from medication.

Step-down approach usually implies the use of potent medications like PPIs in adequate doses and then decreasing the dose or switching to an H2RA as the condition improves. It is employed in endoscopically proven severe GERD or if there are red flags indicating the presence of severe disease. The advantages to this approach are institution of very effective therapy in patients warranting aggressive treatment. It might even be more cost-effective by avoiding potential need for surgery in patients with complications of severe disease.

Common Pharmacologic Agents

Histamine Type 2 Receptor Antagonists

H2RAs reduce gastric acidity by inhibiting the histamine type 2 receptors in the gastric parietal cells. They tend to have a moderate effect on symptoms and healing in patients with esophagitis and are not very effective for severe erosive esophagitis. Their effect appears to be dose related. The knowledge that histamine resulted in gastric acid secretion led to the discovery of cimetidine, the first H2RA introduced in the late 1970s. Other agents subsequently introduced were ranitidine, famotidine, and nizatidine.

Pharmacology

Cimetidine is a 2-cyano- 1-methyl-3-(2-[(5-methyl- 1*H*-imidazol- 4-yl) methylthio] ethyl) guanidine. Replacement of the imidazole ring of cimetidine with furan ring resulted in the development of ranitidine and replacement of the imidazole ring with a 2-guanidinothiazole ring resulted in famotidine. These substitutions resulted in much better tolerability, longer-lasting action, and increased activity. Nizatidine was formed by the substitution of the furan ring of famotidine with a thiazole ring. In general, the latter three are much more potent than cimetidine.

Cimetidine and ranitidine show peak plasma concentration within 90 min of oral administration [21, 22]. They start reducing gastric acidity within 30 min of ingestion. H2RA reduce acid secretion stimulated principally by histamine and to a small extent that by gastrin and cholinomimetic agents through two mechanisms. First, histamine released from enterochromaffin-like (ECL) cells by gastrin or vagal stimulation is blocked from binding to the parietal cell H2-receptor. Secondly, in the presence of H2-receptor blockade, gastrin or acetylcholine has a diminished effect on acid secretion by direct stimulation. H2RAs are particularly effective at inhibiting nocturnal acid secretion, which depends largely on histamine. They have a modest impact on meal-stimulated acid secretion which is stimulated by gastrin and acetylcholine, as well as histamine. The H2RAs suppress acid secretion in a linear, dose-dependent manner [23, 24]. The volume of gastric secretion and the concentration of pepsin are also reduced.

Cimetidine, ranitidine, and famotidine have high first-pass metabolism reducing their bioavailability to about 50 %. Nizatidine undergoes very little first-pass metabolism and has a higher bioavailability [25]. Meals do not affect the bioavailability of H2RAs, but concurrent administration of antacids reduces their bioavailability by 10–20 %. Their effect lasts for about six hours. The response can be prolonged by administering more frequent or higher dose. Intravenously administered H2RAs have a 100 % bioavailability, and therefore, the dose has to be adjusted depending on the route. H2RAs can be effectively administered mixed in parenteral nutrition solutions [26]. H2RA cross the blood-brain barrier and are also secreted in breast milk [27].

H2RAs are cleared by a combination of hepatic and renal mechanisms. Cimetidine is principally metabolized in the liver and then excreted by the kidneys. Famotidine, ranitidine, and nizatidine rely on glomerular filtration and renal tubular secretion for their excretion. Therefore, the dose of all H2RA has to be decreased in renal failure and in premature neonates. The dose does not need to be adjusted in liver disease [1].

Toxicity

H2RA are generally considered to be very safe [28]. However, there are side effects that can mainly be categorized as idiosyncratic reactions, those due to drug-induced hypergastrinemia, and drug-induced hypochlorhydria.

Commonly reported side effects include headache, constipation, nausea, and skin rash. Cimetidine has the highest side effect profile of all the drugs in this class. H2RAs can be associated with different CNS side effects like confusion and mental depression. Cimetidine can especially cause these symptoms in patients with liver failure or renal impairment. In young children and infants, H2RAs can cause symptoms of irritability, headbanging, headache, or sleepiness. Unless the clinician is vigilant, these adverse reactions can be misconstrued as a manifestation of reflux and might result in even a higher dose being prescribed [29]. H2RAs can cause idiosyncratic and immune-mediated reactions like myelosuppression, hemolytic anemia, interstitial nephritis, and fever [30–33]. Cimetidine binds to androgen receptors and results in gynecomastia and other antiandrogen effects in adults [34]. These are generally not seen with other H2RAs.

Prolonged acid suppression has been associated with hypergastrinemia in animal studies [35]. Increased gastrin results in proliferation of enterochromaffin cells, which have been associated with carcinoid tumors [36]. However, its clinical significance in humans has not been demonstrated. Acid in the stomach serves as one of the primary lines of defense against ingested microbes. Prolonged acid suppression has been

associated with increased rates of community-acquired pneumonia in adults and children [37], gastroenteritis in children including *Clostridium difficile* [38, 39], candidemia, and necrotizing enterocolitis in preterm infants [40]. Decreased acid secretion has also been tied to vitamin B12 deficiency in adults [41].

Drug Interactions

Cimetidine binds to the cytochrome P450 enzyme in the liver which is responsible for metabolizing several other drugs. Therefore it may decrease metabolism of a wide number of drugs that rely on this pathway. These include cisapride, anticonvulsants, and benzodiazepines. Ranitidine does not bind avidly to the microsomal cytochrome P450 system and therefore does not interact with medications processed through this pathway. Famotidine and nizatidine do not bind to cytochrome P450 [42].

H2RAs can decrease the absorption of antifungals, cephalosporins, and certain iron compounds that rely on the gastric acidity for conversion to the ferrous form. Acid suppression can also decrease the effect of mesalamine preparations that are pH dependent by causing their premature release.

Drug Resistance

Prolonged use of H2RAs orally or parenterally has been shown to lead to tolerance of their antisecretory effect. A study analyzing intravenous ranitidine in children found loss of the antisecretory effect after 6 weeks of therapy [43]. Tachyphylaxis has been demonstrated in healthy adults with cimetidine, ranitidine, famotidine, and nizatidine [44]. Another study in adults demonstrated rapid development of tolerance over 1–2 weeks. With H2RA given in a single evening dose, tolerance was only evident during the night, whereas tolerance occurred throughout the day and night with the three- and four-times-a-day regimens [45].

Proton Pump Inhibitors

Proton pump inhibitors are very strong acid suppressants and are used in a wide variety of acid peptic disease [46]. They irreversibly inhibit the proton pump, thus blocking the effect of any stimulation for the life of the pump. There are six main PPI drugs: omeprazole, lansoprazole, rabeprazole, pantoprazole, esomeprazole, and dexlansoprazole.

Pharmacology

Omeprazole, lansoprazole, and pantoprazole contain as their core structure, 2-pyridyl methylsulfinyl benzimidazole.

These PPIs differ in their substitution patterns. They are basic compounds with a pKa of around 4.0 (except rabeprazole, with a pKa of 5), becoming activated when the pH of the medium is below their pKa [47]. The rate of conversion to the active form is inversely proportional to the pKa; rabeprazole is the PPI with the highest rate of conversion, followed by omeprazole, lansoprazole, and pantoprazole [48].

After oral administration, the PPIs are absorbed as prodrugs in the small bowel and enter the gastric parietal cells, from where they reach the extracellular canaliculi. At this site, due to the acid medium, they are transformed into the active form, which selectively and irreversibly binds the proton pumps.

Proton pumps (K^+-H^+ ATPase) situated in the parietal cell triggered by a cascade in response to three main stimuli, namely, histamine, acetylcholine, and gastrin. The pumps transport the H^+ ion against the steepest concentration gradient in the body, of 3,000,000:1. Chloride is diffused into the canaliculi of the parietal cell, to join with the H^+ ion to produce hydrochloric acid. The pump is a member of the ion transporting, P-type ATPase family or the ion-motive-phosphorylating ATPase family [49]. This family extends from bacteria to mammals. The classification depends on finding that ion-transport is coupled to a cycle of phosphorylation and dephosphorylation of the enzyme. It is made of two subunits: a larger catalytic alpha subunit responsible for the transport and catalytic functions and a smaller 300 amino acid beta subunit responsible for structural and membrane-targeting functions. The pumps have a relatively large cytoplasmic domain, a membrane domain, and a small extracytoplasmic

domain. The latter two domains are relevant to the mechanism and design of acid pump inhibitors.

The drugs designed to inhibit the pump, bind to it covalently. Thus, the pump has to be synthesized de novo to reestablish acid secretion, though some loss of compound may also occur. The pump half-life has been shown to be about 72 h [50]. The formation of disulfide bridges between the PPI and cysteine residues of the alpha subunit of the ATPase produces inhibition of acid secretion for up to 36 h [51]. The proton pumps are in an inactive state in cytoplasm. After stimulation, such as a meal, the pump is translocated to the membrane of the canaliculus, where it is activated. To inhibit this, omeprazole must reach a sufficient plasma concentration.

The pump turnover however is a dynamic process that varies by the canalicular: tubular ratio of the parietal cell [49]. In a generally stimulated state of the parietal cell, most of the pump population is present in the secretory canaliculus, while in the resting state, the pump is in the cytoplasmic tubules and not associated with the canaliculus. Since the major degradative pathway for the pump, inhibition of acid secretion, which generates decreased canalicular area, leads to decreased pump turnover as occurs with acid blocking agents such as ranitidine. Thus pump inhibitors that change the distribution between tubules and canaliculi change the half-life of the pump.

The duration of suppression of acid secretion does not depend on the peak concentration reached but on the area under the plasma concentration-time curve of the drug. The increase in the dose or the decrease in the dosage interval produces a nonlinear increase in the area under the curve (AUC) of omeprazole. This fact is due to the slower clearance and the effect of the hepatic metabolism [51].

Summary of Pharmacokinetics

These drugs are absorbed rapidly from the gastrointestinal tract. The time needed to reach the peak plasma concentration varies for the different kinds of PPIs.

In the case of immediate release formulations, the T-max was as short as 10 min and from 30 to 300 min for delayed release formulations. The T-max is longest for rabeprazole and shortest for immediate release omeprazole. After absorption, it is rapidly eliminated from the plasma, and in most cases, all the active drug is metabolized in 3–4 h.

The effect of reducing the acidity as measured by the effective time pH remains above 4 is not affected by the plasma drug concentration [52]. It appears to be related to the AUC. Thus in most cases, the drug is rapidly eliminated from the system, but the effect lasts 3–4 days.

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86 Mucosal Protective Agent: Sucralfate in the Treatment of Gastroesophageal Reflux Disease in Children

M. Smits and Marc A. Benninga

Introduction

Sucralfate is a mucosal protective coating agent that binds selectively to damaged or inflamed tissue to form a protective barrier. Sucralfate is a basic aluminum salt of sucrose octasulfate. At an acid pH, it forms large complexes with proteins (primary albumin and fibrogen) that adhere to the damaged tissue to prevent back diffusion of gastric acid, pepsin, and bile salts. Sucralfate also inhibits the direct binding of pepsin to ulcer protein and absorbs bile acids.

Another important effect of sucralfate is stimulating the bicarbonate and mucus production by gastric mucosa and the enhancement of cell renewal, the latter by stimulating the increase of prostaglandin E2, epidermal growth factors (EGF), and basis fibroblast growth factors (bFGF).

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Despite its aluminum hydroxide components, sucralfate does not alter the gastric pH and thus does not work as an antacid at a normal therapeutic dosage. Also the drug has no apparent effect on gastric acid secretion, gastrin release, or upper gastrointestinal motility.

Pharmacodynamic Properties

Sucralfate is only minimally absorbed from the gastrointestinal (GI) tract, due to its pour solubility and high polarity. Over 90 % of orally administrated sucralfate leaves the GI tract unaffected with the feces.

Studies in animals show that 3–5 % of an oral dose of sucralfate reaches the systemic circulation as sucrose sulfate, which is excreted unchanged in the urine within 48 h. In animals, the elimination half-life of sucrose sulfate ranges from 6 to 20 h.

Since sucralfates act as a therapeutic agent on site of the damaged mucosa, its effect depends on the time the drug stays in contact with these erosions. Binding to the ulcer site has been demonstrated for up to 6 h following oral administration, and 30 % of the dose is retained within the GI tract for at least 3 h.

Pharmacokinetic Properties

Sucralfate has been shown to interact with several types of drugs. These interactions appear to be non-systemic and most likely result from

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binding of the drug to sucralfate in the GI tract. The following agents may be less absorbed due to interaction with sucralfate: ciprofloxacine, warfarin and possibly other anticoagulants, digoxin, phenytoin, tetracycline, naproxen, norfloxacin, and antacids. Therefore, it is suggested not to ingest these agents concomitantly with or within 2 h of a dose of sucralfate.

Clinical Efficacy

Only one clinical trial evaluates the use of sucralfate in management of esophagitis caused by gastroesophageal reflux in children [1]. A total of 75 children from 3 months to 13 years were divided into three groups and treated with either sucralfate suspension, sucralfate tablets (dosage <6 years, 0.5 g four times a day; >6 years, 1 g four times a day), or the H2 receptor antagonist, cimetidine, dosage 20 mg/kg a day in two doses. All groups improved or showed endoscopic healing. Furthermore, in all groups, a decrease in symptoms was seen, but no significant differences between the groups were found. Based on this study in children, it is however difficult to state that sucralfate is effective in children from 3 months to 13 years, since there is a lack of placebo-controlled trials.

In adults, several studies have evaluated the effect of treatment with sucralfate in reflux esophagitis. It seems sucralfate (1 g orally before meals and bedtime) is equivalent to alginic acid/antacid and H2RA in endoscopic and symptomatic improvement and healing of esophagitis [2, 3]. However, these studies are often limited by their relatively small size (40–70 patients) and lack of placebo control. Simon et al. [4] found a statistically proved superiority of sucralfate gel compared to placebo in adults with non-erosive gastroesophageal reflux disease (NERD). Recently, Moayyedi et al. reviewed the effectiveness of several medical treatment options in the short-term management of reflux esophagitis in adults, including mucosal protective agent sucralfate [5]. They concluded there is no statistically significant benefit of taking sucralfate compared to antacid or placebo in healing of esophagitis (relative risk of persistence at 6 weeks, 0.82; 95 % CI, 0.67–1.01).

Sucralfate has been shown effective in preventing the development of stress ulcerations in critically ill patients and can be used topically to treat mucosal lesions from various origins (i.e., in recurrent aphthous stomatitis and epidermolysis bullosa) [6, 7].

Tolerability

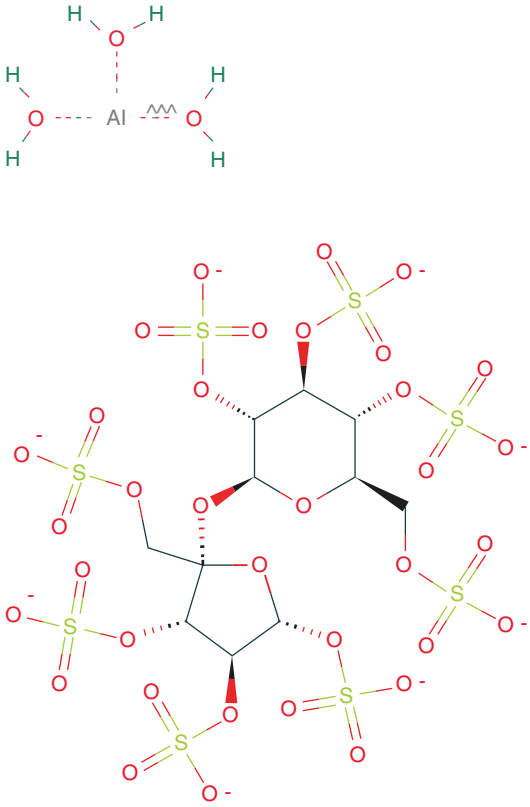
Treatment with sucralfate has little side effects, the only major one being constipation, which occurs in 2–3 % of patients. Nausea and headaches occur less often. Sucralfate can cause serious adverse effect such as bezoars, especially when given to premature, neonates, and critically ill patients [8]. Although aluminum uptake in patients with normal renal function is not significantly increased under sucralfate treatment, it is advised to use an alternative agent in children and adults with (acute) renal failure, as their plasma aluminum levels can reach toxic levels during sucralfate therapy [9–11]. The chemical structure of sucralfate may cause interactions with other drugs (see pharmacokinetic properties). To minimize the risk of interaction or decreased absorption, it is recommended to take sucralfate at least 2 h apart from other drugs.

Dosage and Administration

Sucralfate is available in suspension and tablets, which are usually dosed at 1 g four times a day (before each meal and bedtime). In children under 6 years of age, the recommended dose is 0.5 g four times a day [1]. Since the tablets often need to be dissolved in water and the suspension is generally well accepted, the latter might be the preferable form of administration in children.

Systematic Name and Chemical Structure of Sucralfate

Aluminum, [(2R,3S,4S,5R)-2,4-disulfonatooxy-5-(sulfonatooxymethyl)-5-[(2S,3R,4S,5R,6R)-3,4,5-trisulfonatooxy-6-(sulfonatooxymethyl)oxan-2-yl]oxyoxolan-3-yl] sulfate, and trihydrate



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87 Antacids and Alginates in the Treatment of Gastroesophageal Reflux Disease

R.E. van der Pol and Marc A. Benninga

Introduction

Antacids neutralize gastric acid and are, partly due to their over-the-counter availability, broadly used in the treatment of gastroesophageal reflux disease (GERD) in adults. They are utilized for more than 2,000 years, though evidence of the effectiveness and safety is limited in infants [1]. Antacids have an effect on the short-term relief of heartburn and the healing of esophagitis. Characteristic antacids consist of alkali complexes of aluminum and/or magnesium, aluminum and magnesium phosphates, magnesium trisilicate, carbonate, and bicarbonate salts [2]. Alginate-based raft-forming formulations vary from conventional antacids by forming a gel on the surface of the gastric contents and contain sodium or potassium bicarbonate. Alginates and antacids components are frequently combined in one product. Because of potential toxicity, prolonged use of antacids should be avoided [3].

Pharmacodynamics and Pharmacokinetics

Antacids act locally and instantly by buffering gastric contents. An incline in pH can be accomplished within minutes. Nonetheless, the antacid is not capable to retain the elevated pH despite gastric emptying rate and continued acid secretion [4]. Alginates contain polysaccharide polymers derived from brown seaweed. In contact with the acid environment of the stomach, alginates form a viscous gel. Combined with an antacid, generally a bicarbonate, the antacid generates carbon dioxide (CO_2) after reacting with the acid gastric contents. The carbon dioxide bubbles up and becomes entrapped in the viscous gel making the raft float. In this manner, a near-neutral barrier exists between the esophagus and the acid compounds of the stomach providing an immediate onset of effect [1, 5–7]. A special alginate for children exists as well (Gaviscon® Infant) containing sodium, magnesium alginate, and mannitol. It does not contain bicarbonate; hence, a "raft" is not formed and acts as a feed thickener instead [8].

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Clinical Efficacy of Antacids

Little evidence of the clinical efficacy of antacids in children exists. In a comparative trial involving 33 children (2–24 months old) with GERD and/or esophagitis, high-dosed antacid showed to be as effective as cimetidine [9]. However, all cases of esophagitis were mild, without erosions or lesion. In another RCT, 80 children with severe gastroesophageal reflux were randomly divided into four groups: group A was treated with domperidone plus magnesium hydroxide and aluminum hydroxide, group B with domperidone plus alginate, group C with domperidone alone, and group D received placebo [10]. At the time of diagnosis and 8 weeks after treatment, patients were clinically evaluated and underwent 24-h pH measurement. After treatment, a complete regression of symptoms was observed in 80 % of patients in group A, in 40 % in group B (A versus B, $p<0.018$), in 45 % in group C (A versus C, $p<0.034$), and in 35 % in group D (A versus D, $p<0.001$). Furthermore, reflux parameters according to pH measurement were significantly lower in the group receiving domperidone with magnesium and aluminum hydroxide compared to the other groups. Yet a significant improvement in all treatment groups was found. Despite widespread use of antacids in adults, definitive evidence of their therapeutic benefit in the treatment of GERD is limited by the paucity of well-designed, large, placebo-controlled trials as well. For the placebo-controlled studies that are available, results are conflicting [11]. In conclusion, antacids might be effective in the treatment of GERD yet valid, sufficient evidence is lacking.

Clinical Efficacy of Alginates

The effect of alginates in children has been studied to a greater extent. A randomized, placebo-controlled, double-blind study using combined pH and impedance measurement in 20 children (between 34 and 319 days old) with gastroesophageal reflux showed no differences in the median number of reflux events/hour, acid reflux events/hour, minimum distal or proximal pH, total acid clearance time per hour (time with pH below pH 4), and total reflux duration per hour between Gaviscon and placebo. Only a minimal, though significant, difference in average reflux height was found [12]. In this study, Gaviscon Infant was used, which, in contrast to the adult form of Gaviscon, does not contain bicarbonate and therefore does not form a raft but acts as a thickening agent. The Del Buono et al. data are in accordance with an earlier study evaluating the effects of thickened feeding on GOR in infants [13]. Wenzl et al. found a reduction in reflux height in patients after they were fed with thickened milk as well. Furthermore, no difference was observed in acid reflux events before and after treatment [13].

In a double-blind, randomized, parallel-group study, conducted at 25 centers in the UK, 90 pediatric patients aged 0–12 months, with gastroesophageal reflux, were recruited in a general practice setting. For the primary efficacy measure, number of vomiting/regurgitation episodes, alginate was significantly superior to placebo ($p=0.009$) [14]. Furthermore, patients receiving alginate achieved superior assessments of treatment outcome by both investigators ($p=0.008$) and parent/guardians ($p=0.002$). The safety profile of alginate was similar to that of placebo [14]. The limitation of this study was that no pH and impedance measurement was performed and a relatively short follow-up period [14]. Two older studies both using pH monitoring described conflicting results [15, 16]. Buts et al. studied 20 infants and children with characteristic symptoms of GERD. Patients were divided at random into two groups which were given either Gaviscon (ten patients, mean age, 21 months) or a placebo (ten patients, mean age, 35 months) for eight consecutive days. Parents reported a decrease of regurgitation episodes during Gaviscon therapy, while no clinical improvement was reported in the placebo group [15]. In contrast, Forbes et al. included 30 infants and children, ranging from 4 months to 17 years with GERD. Patients were randomized to receive metoclopramide, alginic acid with antacid (Gaviscon Infant liquid), or a placebo. Disappointingly, neither metoclopramide nor the alginic acid-antacid compound showed a reduction in the frequency or duration of gastroesophageal reflux [16]. In conclusion all these studies clearly show that there is a lack in well-

designed large placebo-controlled trials evaluating the effect of alginates in the treatment of infants and children with GERD.

Tolerability

Aluminum-containing antacids, when used persistently, can raise plasma aluminum in infants. Several studies in children described plasma aluminum concentrations within reach of levels associated with rickets, microcytic anemia, osteopenia, and neurotoxicity. Constipation as well as diarrhea can occur with magnesium-rich preparations [3]. High dosage or prolonged use of calcium carbonate has the potential to result in milk-alkali syndrome, a triad of hypercalcemia, alkalosis, and renal failure [3]. Aluminum and magnesium containing antacids might chelate drugs in the upper gastrointestinal tract. Drugs to interact in this manner include quinolone antibacterial agents, didanosine, azithromycin, tetracycline, and H2 antagonists. To avoid any interaction, separating the time of administration by 2 h should suffice [17].

Dosage and Administration

The time of intake is of great significance because of the rapid onset of action for both antacid and alginates. Optimal benefit is accomplished while taken in the postprandial period when gastric emptying time is prolonged [1]. Antacids in a dose of 0.5 ml/kg have shown to be effective [18]. Special care is warranted in children with renal impairments since antacids have the possibility to heighten serum aluminum levels.

Conclusion

Antacids and alginates may be useful in the short-term treatment of GERD, although there is a paucity of valid evidence-based proof and result is often inconsistent. Long-standing utilization of antacids should not be advocated because the risk of possible side effects and the availability of other, more properly studied and saver options in the treatment of gastroesophageal reflux disease.

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88 Histamine-2 Receptor Antagonist in the Treatment of Gastroesophageal Reflux Disease

Herbert M. van Wering and Marc A. Benninga

Introduction

In the stomach, gastric acid is secreted by the parietal cell. Several factors such as the presence of food, the smell, and/or taste of food and stress have influence on gastric acid secretion. Gastrin, histamine, acetylcholine, and prostaglandin regulate gastric acid secretion through the gastrin, the histamine, the muscarine, and the prostaglandin receptors, respectively (Fig. 88.1). In contrast, the prostaglandin receptor downregulates the gastric acid secretion and protects against the erosive irritation of gastric acid. The presence of food raises the pH in the stomach, which stimulates gastrin cells in the antrum of the stomach to produce gastrin. Subsequently, gastrin is then excreted into the bloodstream and stimulates the receptors at the parietal cell (the direct pathway) as well as the receptors at the adjacent endocrine cell (the histamine pathway). Acetylcholine (neurotransmitter) has a similar working mechanism and demonstrates the neural influence on gastric acid secretion. Histamine is produced by the endocrine cells and stimulates the histamine-2 receptor at the adjacent parietal cells. This stimulation results in an increase of intracellular cAMP, which in turn activates the H^+/K^+-ATPase. Also at the parietal cell, the acetylcholine binds and activates the acetylcholine receptor, which results in the opening of calcium channels. This leads to a calcium influx. In addition, gastrin binds and activates the gastrin receptors, which results in the mobilization of the intracellular calcium pool. These two additional mechanisms help the cAMP to activate the H^+/K^+-ATPase. This process will actively shift H^+-ions into the lumen of the stomach in exchange to K^+-ions (Fig. 88.1). The histamine, gastrin, acetylcholine, and prostaglandin receptors together form a mechanism to balance the gastric acid production for the digestion of food and the downregulation for the protection of the esophagus, stomach, and duodenum.

Pharmacological Properties of Histamine

Histamine stimulates the H_2 receptors and plays a key role in the mechanism of gastric acid production. Histamine-2 receptor antagonists (H_2RAs) have affinity for the H_2 receptors and inhibit the interaction of histamine (Fig. 88.1). Therefore,

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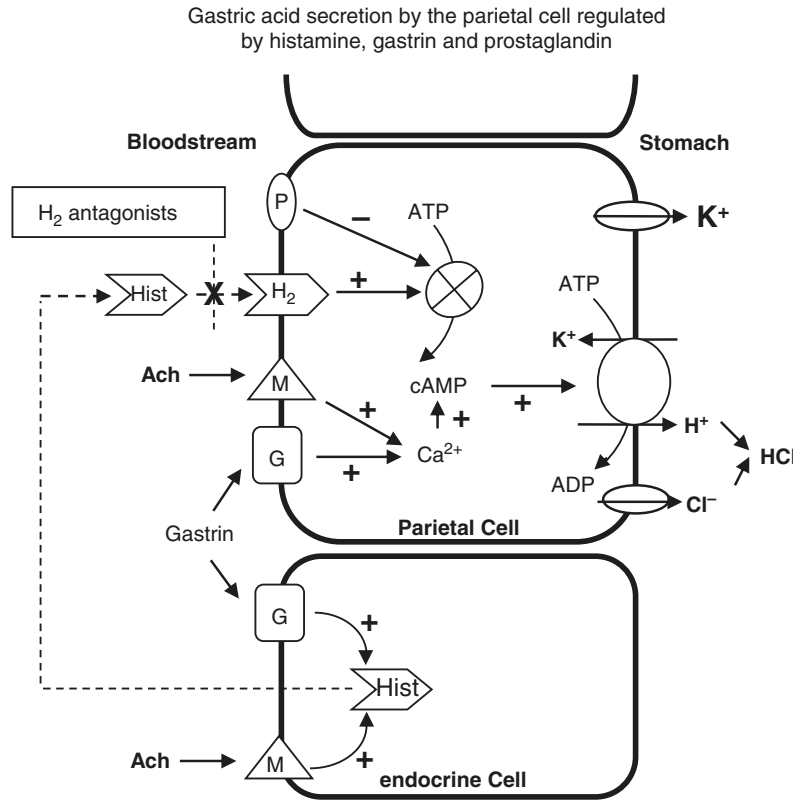

Fig. 88.1 Simplified illustration of gastric acid regulation by histamine, gastrin, and prostaglandin. *Hist* histamine, H_2 H_2 histamine receptor, *P* prostaglandin receptor, *M* muscarine cholinerge receptor, *G* gastrin receptor, *cAMP* cyclic AMP, Ca^{2+} intracellular calcium pool. The H_2 antagonist competitively inhibits the interaction of histamine at the H_2 histamine receptor illustrated by X

H_2RAs are a suitable selective drug to inhibit gastric acid secretion. In 1976, cimetidine was the first H_2RA that became available for clinical use in adults [1, 2]. Hereafter, other H_2RAs have become available, like ranitidine [3], famotidine [4], and nizatidine [5]. In adult patients the dosage, pharmacokinetics, and efficacy of H_2RA have been established; side effects and complications are well known and infrequent in occurrence. H_2RAs each have specific structural differences (Fig. 88.2), pharmacokinetics, and side effects, which give them their unique clinical use. Although in pediatric patients much of the data is based on small studies, ranitidine [6–9] and cimetidine [10, 11] are well characterized. In contrast, famotidine [12], and nizatidine [13] are less familiar, and the treatment specifics need to be explored more.

Mechanism of Action

H_2RAs inhibit the gastric acid secretion that is regulated by histamine, in a dose-dependent and competitive manner. The effect of inhibition is linear to the concentration of the drug in plasma over a wide range. Since the histamine production is influenced by gastrin and acetylcholine (Fig. 88.1), H_2RAs also inhibit to a lesser extent their influences. Therefore, H_2RAs inhibit the stimulated gastric acid production (in the presence of food) as well as the spontaneous basal (fasting) and nocturnal acid secretion. H_2RA reduces the H^+ concentration in the gastric acid juice as well as the volume of the gastric acid juice. Additionally, the pepsin output is reduced, since the production of pepsin generally falls in parallel with the volume of gastric acid secretion. Furthermore, the intrinsic factor secretion is reduced. Since this secretion is normally in great excess, vitamin B_{12} absorption remains usually adequate. In general, H_2RAs have a wide therapeutic usage in adults as well as in children: gastroesophageal reflux, acid or peptic disease, gastritis or esophagitis with or without hemorrhage, cystic fibrosis with maldigestion, and postoperative hypersecretion after small bowel reduction.

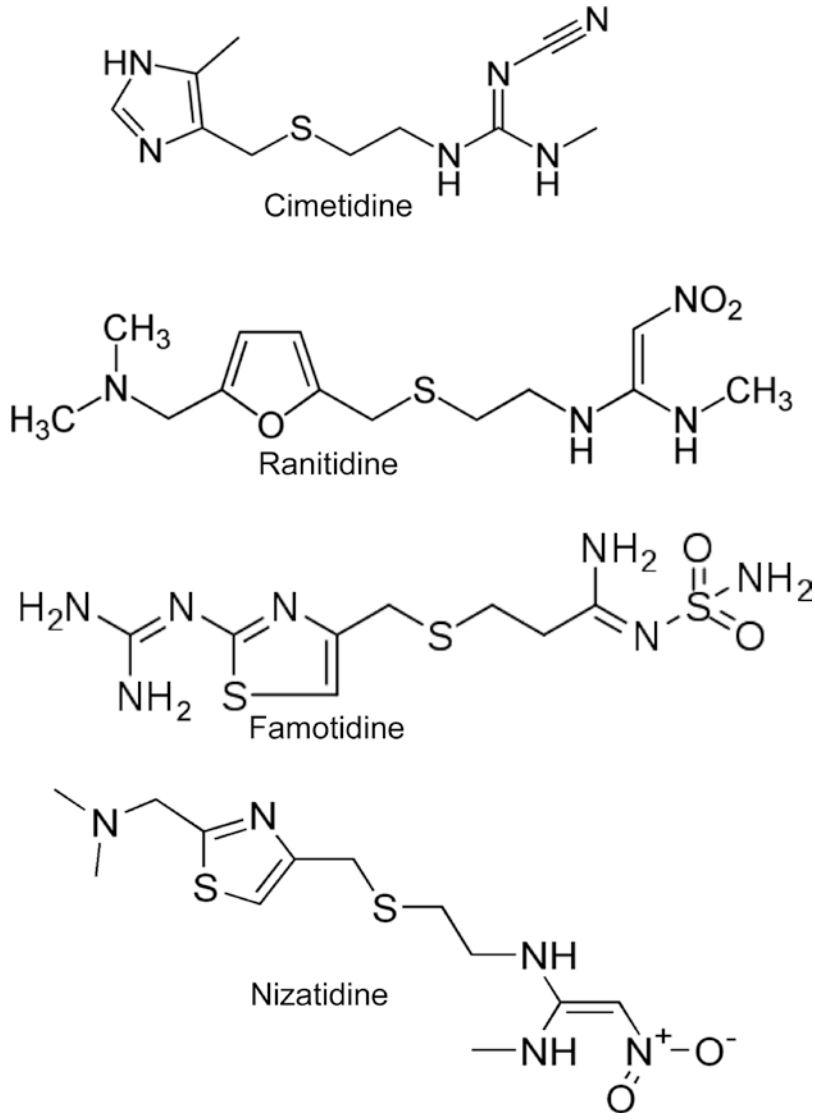

Fig. 88.2 Chemical structure of cimetidine, ranitidine, famotidine, and nizatidine

Pharmacokinetics and Pharmacodynamics

H_2RA pharmacokinetics in adults is similar to the pharmacokinetics in pediatric patients. Taken orally, H_2RAs are quickly and almost completely absorbed. Ranitidine and cimetidine have been extensively described in newborn infants, toddlers, children, and critically ill children [6–11]. In general, both drugs have a shorter half-life and a larger volume of distribution in children compared to adults. Also, children have a higher renal clearance than adults. Ranitidine is pharmacological similar to cimetidine but contains an amino methyl furantoin moiety instead of an imidazole nucleus (Fig. 88.2). This structural difference implies that ranitidine is 5–12 times more potent than cimetidine on a molar basis [14]. The half-life, volume of distribution, and clearance values of ranitidine are similar after an intravenous bolus or an oral dose (1.8 vs 2.0 h, 2.3 vs 2.5 l/kg and 794.7 vs 788 ml/min/1.73 m^2, respectively) in children (3.5–16 years). Due to a significant first-pass effect, the bioavailability of ranitidine averages 48 % in children, and the peak serum concentration is reached after almost 2 h [6]. Around 70 % of ranitidine is metabolized

into nitrogen, sulfoxide, and desmethyl derivat and cleared in the urine. The half-life, volume of distribution, and body clearance values in newborn infants are 3.45 (±0.3) h, 1.52 (±0.91) l/kg, and 5.02 (±0.46) ml/kg/min, respectively [7]. The half-life and clearance in critically ill children are 3.01 (±1.35) h and 8.5 (±3.7) ml/kg/min [8]. Patients with cystic fibrosis have slightly altered pharmacokinetics. The half-life in these patients is 2.7 (±1.4) h, steady-state volume of distribution is 4.6 (±1.7) l/kg, and plasma clearance is 17.03 (±4.8) ml/kg/min [15]. In pediatric patients, the serum concentration around 40–60 ng/ml is necessary to suppress gastric acid secretion by 90%; these concentrations are achieved by an oral dose of 1.25–1.9 mg/kg every 12 h [6].

The cimetidine disposition is best described by a biphasic elimination curve half-life time for cimetidine, and its metabolites: cimetidine sulfoxide and hydroxymethyl cimetidine of 1.39, 2.6 and 4.7 h, respectively, in adults. The body clearance in pediatric patients is higher due to a better renal clearance11.6 ± 3.4 ml/kg/min versus 7.0 ± 2.5 ml/kg/min in adults [16]. Around 70% of the cimetidine is cleared into the urine. After an oral or iv bolus, the half-life and the volume of distribution are 1.38 (±0.43) h and 1.24 ± 0.4 l/kg, respectively, in children (4–13 years) [16]. The half-life of cimetidine in newborn infants ranges from 1.10 to 2.18 h [17]. In critically ill children, the mean apparent volume of distribution and total body clearance are 1.23 l/kg and 10.4 ml/kg/min [18]. The correlation between serum concentration and pH reduction in the stomach is uncertain. Lambert et al. [11] described that after a 10 mg/kg oral dose of cimetidine, 75% of the pediatric patients had a significant gastric acid suppression after 2 h.

The pharmacokinetics and pharmacodynamics of famotidine in children are similar to adults [19]. The famotidine pharmacokinetics are investigated mainly by an intravenous administered dosage in children (>1 years old) [20] and infants [21]. Famotidine is primarily eliminated by glomerular filtration and active renal secretion. In children and adults, between 67% and 73% is eliminated unchanged in the urine within the first 24 h. The inactive sulfoxide is one of the metabolized by-products. In children >1 years of age, the elimination half-life is 3.2 ± 3.0 h and volume of distribution is 2.4 ± 1.7 l/kg. The plasma clearance and renal clearance are 11.7 ± 5.7 ml/kg/min and 7.2 ± 4 ml/kg/min, respectively. Infants younger than 3 months old have a significant decreased plasma and renal clearance, but infants older than 3 months of age are similar to the older children [20]. Also, famotidine renal clearance is diminished significantly in patients with renal failure; accordingly, dosing should be based on glomerular filtration rate [22]. Pharmacodynamic analysis demonstrated that 50% of the maximal effect of famotidine occurs at a serum concentration of 26.0 ± 13.2 ng/ml [19].

The pharmacokinetics of nizatidine in children is similar to the pharmacokinetics in adults [23]. The bioavailability of nizatidine is approximately 70% in adults. This was comparable to the bioavailability in children, who coingested the drug with fruit/vegetable juice. The terminal elimination rate for nizatidine in pediatric patients is 0.58 ± 0.8/h [24]. Nizatidine is 90% excreted unchanged into the urine.

Side Effects and Drug Interactions

H_2RAs are highly selective for the H_2 receptors, and they have little effect on H_1, H_3, or H_4 histamine receptors. Although H_2 receptors are present in numerous tissues, including bronchial smooth muscle and vascular system, they are very seldom inhibited by H_2RAs. Recently, it has been described that any gastric acid inhibitors (H_2RA as well as proton pump inhibitors) raise the risk of acute gastroenteritis [25] and community-acquired pneumonia in children [26]. This increased risk of infection is attributed to the disruption of first-line defense mechanism by the acidic environment of the stomach [27]. In general, any therapy that raises the pH of the stomach alters the absorption rate of weak acidic or weak alkalic drugs [28]. Drugs like cefuroxime, posaconazole, cefpodoxime, as well as itraconazole and ketoconazole are influenced by a higher pH in the stomach. H_2 antagonists may lead to fundamental changes in the absorption

and disposition of other drugs. However, there are similarities and differences between the H_2 antagonists in this respect, depending on the process involved. H_2RAs lower the blood supply of the liver itself, which may inhibit the transformation of drugs with a high first-pass effect, like lidocaine [29]. Cimetidine, but not so much by ranitidine, famotidine, or nizatidine, inhibits the activity of cytochrome P_{450}, thereby slowing the metabolism of many drugs that are substrates for hepatic mixed-function oxidases. Thus, the concentration of drugs like phenytoin, digitoxin, warfarin, and others will be prolonged in the human circulation [28]. The use of ranitidine has been rarely associated with bradycardia [30] and sepsis [31] in pediatric patients. Other general but rare side effects are headache, dizziness, blood count changes, and liver function disruption. Cimetidine has similar side effects, but more frequently and in a wider range compared to ranitidine. Specific side effects of cimetidine are mental confusion, hallucinations, hepatotoxicity, and hypotension. In adult male patients receiving long-term high-dose cimetidine, it has been observed that they develop gynecomastia, loss of libido, and impotence. These effects are presumably described to the antiandrogen working mechanism of cimetidine [32]. These endocrine changes have not been specified in children, although significantly elevated prolactin levels have been shown [33]. These endocrine problems have not been reported with ranitidine, famotidine, or nizatidine. H_2RAs have been investigated during pregnancy and have no effect on major malformations [34].

Clinical Relevance

Although the H_2RA as a group has a selective working mechanism and infrequent side effects, only ranitidine has been extensively investigated and used in pediatric patients. Cimetidine is rarely used in pediatric patients as concerns exist about the effect on cytochrome P_{450} and multiple drug interactions as well as the interference with endocrine function (see pharmacokinetics above). The usage of famotidine and nizatidine has been described in pediatric patients and has some promising usage profile [19–24]. However, these two drugs have only been investigated in very small studies, and more randomized clinical trials are needed to characterize these drugs in pediatric patients. Therefore, famotidine and nizatidine have not been licensed for use in children in the UK and the Netherlands, although they are licensed in the USA. Moreover, ranitidine has a favorable pharmacokinetic profile compared to famotidine [35]. Presently, ranitidine is the most prescribed and recommended H_2RA in a therapeutic role for pediatric patients with gastroesophageal reflux disease [36].

Therapeutic Choices

Ranitidine is widely used in the treatment of children with acid or peptic disease, gastritis or esophagitis with or without hemorrhage [36], cystic fibrosis, postoperative hypersecretion after small bowel resection, and gastrointestinal and pulmonary symptoms caused by gastroesophageal reflux. Gastroesophageal reflux (GER) is a common phenomenon in children, characterized by the regurgitation of the gastric contents into the esophagus. Two recent review articles [37, 38] described the use of ranitidine in GER(D) in children. In summary, for infant GERD ranitidine and omeprazol (PPI) are safe and effective therapy (min. 8–12 weeks) that should provide symptomatic relief and endoscopic and histologic healing of esophagitis. When GERD is refractory to ranitidine, omeprazole demonstrated to be a more effective therapy. In older children ranitidine has similar success rates as omeprazole and is the cornerstone of the therapy for GERD for a minimum of 8–12 weeks [37]. The intermittent use of ranitidine for the treatment of symptoms of GER has been described in children (4–11 years) and demonstrated similarities to adult intermittent treatment effect. This intermittent therapy suppressed the gastric acid production for about 5–6 h [9].

Peptic ulcerations, stress ulceration, and upper GI bleeding have been treated with gastric acid suppression by ranitidine. Recently, data has been published that proton pump inhibitors have

been more successful with less side effects in adults [39, 40].

Other Clinical Usage of H_2RAs

Recksuppaphol et al. have described that a course of ranitidine administered 24 h prior to a Meckel scan improves the sensitivity of this Meckel scan [41]. As part of the triple therapy to eradicate *Helicobacter pylori*, ranitidine has been used extensively, but it has been proven that proton pump inhibitors have a better outcome [42]. Abdominal discomfort in patients with Henoch-Schönlein vasculitis is eased by a treatment with ranitidine as demonstrated by Narin et al. [43]. Others [44] have described the usage of cimetidine orally for the lone treatment of pedal verruca in all age groups.

Dosage and Administration

Oral administration is indicated for GERD, *gastric ulcers and duodenal ulcers* in pediatric patients. The therapeutic regimen in newborn infants is 5 mg/kg/day in two doses and for older children (1 month till 18 years) 6–10 mg/kg daily in two doses, with a maximum dosage of 300 mg/day. Ranitidine has been fabricated for oral use in tablet and syrup, which have an equal effect, but tablets dissolved in water have a better taste, which may lead to a better therapeutic compliance [45]. In the prevention of stress ulcers and as supportive care in gastrointestinal bleeding, ranitidine is given intravenously. For neonates 2.5 mg/kg/day in two doses has been suggested. For older children from 1 month up to 18 years old, 3–6 mg/kg in three to four doses daily has been [38, 46] suggested. The maximum daily dosage is 200 mg. As an alternative, ranitidine can be administered in a continuous intravenous infusion of a total of 4 mg/kg/day. Ranitidine liquids for oral use contain 8 % alcohol. The leads to, when given a maximum dose of 300 mg/day, the patient is also taken 1.6 g of alcohol. This is comparable with 32 ml of beer or 13 ml of wine. One has to keep this in mind when given to patient with liver failure or epileptic seizures.

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Proton Pump Inhibitors

89

Licia Pensabene and Geoffrey Davidson

Introduction

Recent years have seen widespread use of potent gastric acidity inhibitors in the management of many upper gastrointestinal disorders, also in pediatric patients [7]. Acid suppression with PPIs is the standard treatment for GERD and erosive esophagitis in adults and is increasingly becoming first-line therapy for children aged 1–17 years [117]. The potential adverse effects of acid suppression, including increased risk of community-acquired pneumonias and GI infections, need to be balanced against the benefits of therapy [125].

Pharmacological Properties of PPIs

Mechanism of Action

PPIs have become the mainstay of treatment for acid-related gastrointestinal disease in adults since their introduction in 1989 [30]. PPIs have several inherent advantages compared to the older medication classes of antacids or histamine type 2 receptor antagonists (H2RAs). H2RAs reduce acid secretion only by competing with histamine receptors located in the parietal cell membrane; other cellular receptors that respond to endocrine (gastrin) and neuroendocrine (vagal stimulation) pathways are not affected [19]. Thus, H2RAs do not completely block gastric parietal cell acid production.

Unlike H2RAs, PPIs demonstrate consistent gastric pH control and do not develop tachyphylaxis with repeated dosing. PPIs inhibit gastric acid secretion by selectively blocking the gastric parietal cell H+,K+-ATPase (also called the proton pump), an enzyme that is involved in the last step of acid secretion in gastric parietal cells [122]. The superior efficacy of PPIs is largely because of their ability to maintain intragastric pH at or above 4 for longer periods and to inhibit meal-induced acid secretion, a characteristic not shared by H2RAs. The potent suppression of acid secretion by PPIs also results in the decrease of 24-h intragastric volumes, thereby facilitating gastric emptying and decreasing volume reflux [17].

Currently available PPIs are omeprazole, esomeprazole, lansoprazole, dexlansoprazole, pantoprazole, and rabeprazole; they differ in their molecular structure, giving rise to certain differences in their pharmacokinetics [43]. The PPIs are benzimidazole derivatives that differ in their substitution patterns. They are composed of two moieties, a substituted pyridine with a primary pKa of about 4.0, which allows selective accumulation in the acidic space of the secretory canaliculus of the stimulated parietal cell (where

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the pH is about 1.0), and a benzimidazole with a second pKa of about 1.0 [106]. This implies that they are weak bases that will be minimally protonated at neutral pH (of blood) and maximally protonated in environments of high acidity [43]. The rate of conversion to the active form is inversely proportional to the pKa; rabeprazole is the PPI with the highest rate of conversion, followed by omeprazole, lansoprazole, and pantoprazole [103]. PPIs can be considered acid-activated prodrugs that convert to sulfenic acids or sulfenamides that react covalently with one or more cysteines accessible from the luminal surface of the H+,K+-ATPase [67, 106]. Once covalently bound, the H+,K+-ATPase becomes nonfunctional, and activity only returns by parietal cell synthesis of a new H+,K+-ATPase enzyme system [43]. Because of covalent binding, the inhibitory effects of PPIs are longer than expected from their plasma half-life [106]. However, PPIs cannot inhibit all gastric acid pumps with oral dosing since not all pumps are active during the 90-min half-life of the PPI in the blood. PPIs have a short half-life; thus, only 70 % of the pump enzymes are inhibited. About 20 % of pumps are newly synthesized over a 24-h period, and there may be greater pump synthesis at night than during the day. This led many healthcare providers to increase PPI dosing to twice daily. Disappointingly, bedtime administration of PPIs will not add to inhibition of nighttime acid breakthrough [106]. For example, once-daily esomeprazole 40 mg controls acid for a median of 15.3 h daily (after 3–5 days of therapy), and 40 mg taken twice daily (before morning and evening meals) controls acid for 19.5 h daily [30]. In addition, twice-daily PPI therapy has not been tested in appropriately designed trials with clinically significant end points [30].

The proton pumps are in an inactive state in cytoplasm. After stimulation, such as a meal, the pump is translocated to the membrane of the canaliculus, where it is activated. To inhibit this, omeprazole must reach a sufficient plasma concentration. However, the duration of suppression of acid secretion does not depend on the peak concentration reached but on the area under the plasma concentration-time curve of the drug. The increase in dose or decrease in dosage interval of omeprazole produces a nonlinear increase in the area under the curve (AUC) due to slower clearance and the effect of the hepatic metabolism [105].

Metabolism

Omeprazole and the other PPIs are metabolized in the liver by cytochrome P450. The principal enzymes involved in their metabolism are CYP2C19 and, to a lesser degree, CYP3A4, which transform omeprazole into the metabolites 5-hydroxyomeprazole and omeprazole sulfone; 80 % of these metabolites are excreted in the urine. As demonstrated by Kearns et al., there is marked genetic polymorphism of CYP2C19, which directly affects the pharmacokinetics of omeprazole and the other PPIs [67]. Patients can be divided into three groups according to CYP2C19 polymorphism: homozygous extensive metabolizers, heterozygous extensive metabolizers, and poor metabolizers.

The most common, wild-type, homozygous extensive-metabolizer (HomEM) genotype contains two normal (nonmutated) alleles. HomEMs produce an abundance of the enzyme and metabolize the PPI at a higher rate, limiting the drugs' bioavailability [40]. The heterozygous extensive metabolizer (HetEM) contains one wild-type allele and one mutant allele, resulting in the compromised production of the enzyme and, thus, slower metabolism of the PPI [40]. In the poor metabolizer (PM) genotype, both alleles are mutated, which results in a much slower rate of PPI metabolism, ensuring greater bioavailability. A comparison of the ratio of the area under the plasma concentration curve for PPIs shows that HomEM/HetEM/PM is 1:3.7:20 [32]. Thus, PMs have more than five times the PPI available of HetEM and 20 times that of HomEM. This results in a more profound inhibition of gastric acid secretion as measured by intragastric pH [124]. Therefore, extensive metabolizers have a lower AUC than poor metabolizers and therefore require higher doses of omeprazole to achieve

adequate suppression of acid secretion [39]. Furthermore, there is a higher rate of nonresponders among extensive metabolizers [105].

There are marked ethnic differences in the frequency distribution of these genotypes [136]. The Japanese population has an 18–23 % prevalence of PMs. Further, 15–17 % of the Chinese population are PMs and 13 % of Koreans are PMs. The Asian population has a much greater frequency of PM (12–23 %) when compared to Caucasians (1–6 %) and black Africans (1–7.5 %) [136]. The frequency of PMs in African, African-American, and Middle Eastern populations is very similar to Caucasians. Indigenous populations, such as the Canadian Indians and the Australian Aboriginals, have a high frequency of PMs, which is similar to that of the Asian population [136].

Do differences in genotypes have clinically relevant consequences? Few studies [21, 41, 70, 107, 133] do suggest that the efficacy of PPIs in terms of inhibition of acid secretion may be lower in patients who are extensive metabolizers compared with intermediate and PM, but caution is warranted in accepting these conclusions given the low sample sizes of most published studies [20]. A variant of the CYP2C19 has recently been discovered, allele CYP2C19*17, which affects the metabolism of the PPIs, giving its carriers an extensive-metabolizer phenotype. This variant shows racial variations, being found in 18 % of the Swiss and Ethiopian populations and in only 4 % of the Chinese population [105, 108]. The impact of the CYP2C19*17 allele on the pharmacokinetics of pantoprazole and omeprazole in previously studied children ($n=40$) was explored [66]. When pantoprazole area under the plasma concentration versus time curve (AUC) was examined as a function of CYP2C19 genotype, a significantly lower AUC was observed for subjects identified as CYP2C19*1/*1 and CYP2C19*1/*17. For pantoprazole, a statistically significant relationship was observed between CYP2C19 genotype and both the dose-corrected AUC ($p<0.0001$) and the apparent elimination rate constant (K(el); $p=0.0012$); no significant genotype-phenotype relationships were observed for omeprazole [66].

Pharmacokinetics

Pharmacokinetics research in children has not been extensively studied, but suggests that the dose used should be varied as a function of age, as this factor affects the drug's metabolism [109]. The immaturity of various organ systems leads to differences in the pharmacokinetics and efficacy of the PPIs in children compared to adults. The embryonic development of the stomach is completed between 14 and 15 weeks gestation. The mass of parietal cells is responsible for acid secretion and increases with increasing weight and gestational age. H+,K+-ATPase is present by week 25 of gestation and its expression increases with age. Premature infants born after week 24 of gestation are therefore able to maintain an intragastric pH below 4 from the first day of life [11, 78]. Although gastric pH in newborns is slightly higher than in adults, their maximum acid secretion is similar [11]. Gastric emptying (GE) and intestinal motility vary with age, affecting rates of drug absorption [83]. Neonates have slower GE, and lower motility, leading to a greater absorption of drugs in the neonatal age range [130].

The distribution of PPIs can differ in children due to factors such as tissue perfusion, plasma protein concentration, body composition, and variation with age [45, 83]. Hepatic and renal functions also vary with age, affecting drug metabolism and elimination. At birth, there is a low level of activity of the enzymes CYP2C19 and CYP3A4; adult levels of activity are reached in early childhood [75]. At 2 years of age, children have a greater oxidative capacity than adults, whereas glucuronidation develops more slowly. As children approach puberty, their metabolism becomes approaches that of adults [109]. Premature and newborn infants present a lower level of elimination of metabolites, favoring accumulation, whereas this is uncommon in older infants and in children [109]. Furthermore, it is important to note that the metabolic activity, and therefore the pharmacokinetic parameters of the hepatic P450 enzyme systems, will be affected by maturation changes in these systems [2]. These findings corroborate a developmental dependence

in the activity of these enzyme systems, the extent of which is sufficiently significant to alter dose-concentration-effect relationships and, therefore, demand age-specific individualization of dosing to ensure efficacy and safety [75].

Children 1–10 years of age appear to require a higher dose per kilogram for some PPIs than adolescents and adults. Young children require higher per-kilogram doses to attain the same acid blocking effect or area under the curve [3, 78, 134]. This may not apply to all of the PPIs [50]. There is little pharmacokinetic data on PPIs in infants, but several studies indicate that infants younger than 6 months may have a lower per-kilogram dose requirement than older children and adolescents [92, 132]. Thus, multicenter safety and efficacy studies are warranted to assess the most appropriate dosage of PPIs for different pediatric age groups [19].

Bioavailability

Despite their efficacy in the management of acid-related disorders, PPIs have limitations as a consequence of their pharmacologic characteristics [125]. Oral bioavailability of PPIs varies from first to subsequent doses [101]. Omeprazole has a low initial oral bioavailability of 35–40 %, rising to 65 % on repeated administration, whereas lansoprazole, when used in doses higher than 20 mg, has a constant high bioavailability of between 80 % and 91 % and demonstrates linear plasma drug concentrations [43, 101]. Bioavailability of PPIs can be affected by the time of administration in relation to food ingestion [43]. The ingestion of food stimulates proton pumps, so high PPI serum concentrations at the time of meal ingestion result in the most effective acid suppression [30]. PPIs should, therefore, be given at a time that enables their complete systemic absorption before a meal, which is typically 30–60 min beforehand [30]. They must be taken once per day before breakfast and must be protected from gastric acid by enteric coatings. Some studies have shown that food may delay absorption and reduce bioavailability of lansoprazole, even less so for omeprazole (and pantoprazole) [25, 27]. Most available PPIs are therefore regarded as "delayed-release" preparations. Achievement of maximal acid suppression can take up to 4 days [63]. However, a summary of adult data suggests that PPIs can also be used for "on-demand" treatment of symptoms [88]. Dexlansoprazole MR is said to be less dependent on being taken on an empty stomach. Dexlansoprazole, a pure enantiomer of lansoprazole, is a PPI that, with a novel dual delayed-release formulation, provides prolonged inhibition of gastric acid secretion [87] resulting in marked improvements in symptoms of GERD with high maintenance rates and good tolerability [26]. There are no pediatric clinical trials and the drug is not approved for use in children. Pantoprazole is a PPI that has been shown to be safe and effective in the treatment of GERD in adults and children in randomized controlled clinical trials [4, 102, 113]. Pantoprazole has a relatively long duration of action compared with other PPIs, and a lower propensity to become activated in slightly acidic body compartments [90]. Pantoprazole delayed-release granules for oral suspension were developed as an age-appropriate formulation for use in infants and young children unable to swallow tablets [129].

PPIs currently approved for use in children in North America are omeprazole, lansoprazole, and esomeprazole. At this moment, in Europe, only omeprazole and esomeprazole are approved. No PPI has been approved for use in infants younger than 1 year of age. Nevertheless, the number of PPI prescriptions written for infants has increased manyfold in recent years despite the absence of evidence for acid-related disorders in the majority [71, 91, 123]. Although the effectiveness of PPIs in children is under debate, PPI use in infants and children with GERD has increased enormously during the last decade [5, 48].

Current Evidence Regarding PPI Therapy in Different Clinical Settings

GERD Symptoms

Recently published guidelines relating to the diagnosis and management of pediatric gastroesophageal reflux, conducted by the European

Society for Pediatric Gastroenterology Hepatology and Nutrition and the North American Society for Pediatric Gastroenterology Hepatology and Nutrition [125; Sherman et al. 2009], show there are no symptoms or group of symptoms that can reliably diagnose GERD or predict treatment response. Moreover, for mild infant GERD, parental guidance and education combined with feed thickeners and/or positioning therapy will often suffice [122]. However, when pharmacologic treatment is indicated, antisecretory agents play a key role, and usually PPIs are on the front row. However, a recent systematic review of the available evidence underlines that if the primary aim is to treat GERD symptoms in infants, PPIs should not be prescribed [122]. In fact, clinical trials reveal that PPI therapy is not an effective treatment for common infant GERD-associated symptoms [62], despite the finding that acid suppression only occurred in the PPI group [89, 92, 94], maybe because of a lack of specificity of symptom-based diagnosis of GERD in this age group.

In summary, for the reduction of GERD symptoms in infants, PPIs were more effective in one study (lansoprazole was more effective compared with hydrolyzed formula [68]), not effective in two studies (omeprazole compared with a placebo was not effective in reducing GERD symptoms in two studies [89, 92]), and equally effective in two studies (lansoprazole and pantoprazole were equally effective compared with placebo, in two studies [94, 129]). Moreover, evidence supporting safety of PPI use in infants is conflicting [62]. The largest placebo-controlled trial to date [94] found that rates of adverse events were increased in the PPI group compared with the placebo group, whereas the other trials reviewed reported no difference in adverse effects with the use of PPIs. Therefore, if the primary aim is to treat GERD symptoms in infants, PPIs should not be prescribed [122].

Moreover, guidelines [125] underline there is no evidence to support an empiric trial of acid suppression as a diagnostic test in infants and young children where symptoms suggestive of GERD are less specific. In fact, one study of infants with symptoms suggestive of GERD who were treated empirically with a PPI showed no efficacy over placebo [94]. However, expert opinion [125] suggests that a time-limited (2-week) empiric, antisecretory treatment for infants with crying and distressed behavior may be considered if irritability persists with no explanation other than suspected GERD, although clinical recovery may be ascribed to a placebo reaction or physiologic symptom resolution with time.

Extrapolation from adult data suggests that in *older children and adolescents with heartburn*, on-demand therapy with buffering agents, sodium alginate, or H2RA may be used for occasional heartburn [88, 95, 96]. Expert opinion [125] suggests that an older child or adolescent with typical symptoms of *chronic heartburn* should be treated with lifestyle changes if applicable (diet changes, weight loss, smoking avoidance, sleeping position, no late-night eating) and a 2–4-week trial of PPI. The treatment period required to achieve uniform therapeutic responses with PPI therapy probably varies with disease severity, treatment dose, and specific symptoms or complications [120]. The 2-week "PPI test" lacks adequate specificity and sensitivity for use in clinical practice. In an older child or adolescent with symptoms suggesting GERD, an empiric PPI trial is justified for up to 4 weeks [125]. If symptoms resolve, PPIs may be continued for up to 3 months. However, improvement of heartburn, following treatment, does not confirm a diagnosis of GERD because symptoms may improve spontaneously or respond by a placebo effect. In some patients, abrupt discontinuation of treatment may result in acid rebound that precipitates symptoms; therefore, it is recommended that antisecretory therapy be weaned slowly [8, 38]. If symptoms persist on PPI therapy or recur when therapy is weaned or discontinued, upper endoscopy may be helpful to determine the presence and severity of esophagitis and differentiate reflux-related esophagitis from nonreflux pathologies such as infection or eosinophilic esophagitis (EoE) that may present with heartburn [53, 58].

However, a recent systematic review of the available evidence [121] showed that, for *children and adolescents*, PPIs were equally effective in reducing GERD symptoms compared with

what was given in the control groups, alginates, ranitidine, or a different PPI dosage. When comparing the different groups to baseline, GERD symptoms were significantly reduced in all groups [122]. The authors of two studies [9, 24] found that PPIs were more effective at reducing gastric acidity than alginate or ranitidine, but the reduction of macroscopic and histological scores during endoscopy was similar in all study groups (PPI versus ranitidine or alginate) compared with baseline. For gastric acidity, in infants and children, PPIs were more effective (compared with placebo, alginates, or ranitidine) in four studies [24, 89, 92]. For reducing histologic aberrations, PPIs showed no difference (compared with ranitidine or alginates) in three studies [94, 122]. Six studies [49, 93, 113, 118, 129] reported no differences in treatment-related adverse events (compared with placebo or a different PPI dosage). PPIs are generally well tolerated [56] but have some shortcomings and may increase susceptibility to acute gastroenteritis and community-acquired pneumonia [15, 73], respiratory infections [112], gastric polyps [98], and bacterial overgrowth [112]. Despite PPIs seeming to be well tolerated in the short term, there is insufficient evidence to support the effectiveness and safety of PPIs in the treatment of GERD in children and adolescents [122]. Therefore, physicians should be careful when prescribing PPIs, medications that are not approved for infants and have potential adverse effects, unless there is documented disease or with careful monitoring [122].

Reflux Esophagitis

Initial Treatment

In pediatric patients with endoscopically diagnosed reflux esophagitis or established nonerosive reflux disease, PPIs for 3 months constitute initial therapy [125]. For healing of erosive esophagitis and relief of GERD symptoms, PPIs are superior to H2RAs [125]. Initial treatment for 3 months is advised. If adequate symptom control is not achieved within 4 weeks, the dose of PPI can be increased. Patients who require higher PPI dose to control symptoms and produce healing are those with conditions that predispose to severe, chronic GERD and those with higher grades of esophagitis or Barrett's esophagus (BE). In most cases of chronic-relapsing esophagitis, symptom relief can be used as a measure of efficacy of therapy, but in some circumstances repeat endoscopy or diagnostic studies may be indicated.

Most patients require only one daily dose of PPI to obtain symptomatic relief and heal esophagitis [36, 52, 55, 115]. The optimum dosage regimen is a once-daily dose 15–30 min before the first meal of the day; routine use of twice-daily doses is not indicated [125]. When acid suppression is required, the smallest effective dose should be used. It is not necessary to make patients achlorhydric to relieve symptoms or heal esophagitis, and, in light of the data on infections and other complications of acid suppression by H2RAs or PPIs, it is probably not desirable to do so. Not all reflux esophagitis is chronic or relapsing [9], and therefore trials of reduction of dose and withdrawal of PPI therapy should be performed after the patient has been asymptomatic for some time, that is, after 3–6 months on treatment. This approach will minimize the number of children that unnecessarily receive long-term treatment.

PPIs should not be stopped abruptly, because rebound acid secretion may cause recurrence of symptoms [8, 38]. Instead, PPI should be tapered for at least 4 weeks. Recurrence of symptoms and/or esophagitis after repeated trials of PPI withdrawal usually indicates that chronic-relapsing GERD is present, if other causes of esophagitis have been ruled out. At that point, therapeutic options include long-term PPI therapy or antireflux surgery.

In open-label studies of children with erosive esophagitis, PPIs produced healing in 78–95 % with 8 weeks of therapy and in 94–100 % with 12 weeks of therapy. Symptoms improved in 70–80 % of the group treated for 12 weeks [9, 36, 116]. Most patients in these studies had lower grades of erosive esophagitis, and the studies did not include patients with underlying conditions such as NI (define), repaired tracheoesophageal fistula (TOF), chronic lung disease, or hiatal hernia (HH). PPIs have been shown to heal higher

grades of esophagitis (grades 3–4) in children with these underlying conditions, even in some when esophagitis had been refractory to treatment with H2RAs, prokinetic agents, and even antireflux surgery [52, 55, 56]. However, in these selected cases resistant to standard management, high per-kilogram dose and long duration of therapy (up to 6 months) may be required for healing and symptom control [52, 55, 56]. In uncontrolled studies of children with erosive and nonerosive reflux disease (NERD) treated with PPIs, 70 % experienced relief of "typical symptoms of GERD," that is, heartburn [36, 116]. A significant percent of patients remained symptomatic, albeit at lower intensity. Suboptimal symptom relief may be due to large per-kilogram dosing variation. Studies in adults have shown generally poorer therapeutic response to PPI in patients with NERD compared with patients with erosive esophagitis [29, 35].

An international, multicenter, randomized, parallel-group, double-blind (for dose) study showed that an 8-week course of esomeprazole treatment (0.2–1.0 mg/kg) effectively heals macroscopic and microscopic erosive esophagitis in children aged 1–11 years with endoscopically or histologically confirmed GERD. Of 109 patients, 49 % had erosive esophagitis, and 51 % had histologic evidence of reflux esophagitis without erosive esophagitis. Of the 45 patients who had erosive esophagitis and underwent follow-up endoscopy, 89 % experienced erosion resolution [117].

Maintenance Treatment

Although the benefits of short-term treatment with PPIs in pediatric patients with reflux esophagitis has been demonstrated [44, 55, 115], there are few data on long-term maintenance treatment with PPIs in this population. Although the guidelines [125] advocate the short-term use of PPIs in children older than one for the relief of GERD symptoms, the issue of maintenance therapy is not discussed in depth. A recent systematic literature analysis identified five studies that evaluated the *efficacy of PPI maintenance therapy* (6–90-month follow-up) in pediatric patients *after healing of reflux esophagitis* [64]. Of the five relevant studies identified, one was a prospective placebo-controlled study [9], two were prospective single-treatment studies [10, 55], and two were retrospective studies [97, 98]. Three found no relapse of reflux esophagitis or reflux symptoms during PPI maintenance therapy; however, a low relapse rate (1/14) was also found in the placebo group of the only prospectively controlled study. Two of the five studies (both prospective) reported relapse of reflux esophagitis at half the original healing dose of omeprazole (7 of 51 patients relapsed after 3 months; 8 of 32 within 21 months), which resolved again in most patients when the healing dose or higher was given [64]. In the only placebo-controlled prospective study, by Boccia et al. [9], 46 children were randomly assigned after healing of reflux esophagitis (defined as at least grade II according to the Hetzel et al. classification [61]) to a 6-month maintenance therapy with omeprazole, 0.7 mg/kg/day (single daily dose) ($n = 16$), ranitidine, 10 mg/kg/day (divided into two doses) ($n = 16$), or placebo ($n = 14$). Histological, endoscopic, and symptomatic scores were assessed 3 months after discontinuation of maintenance therapy. Reflux esophagitis and reflux symptoms did not relapse in any of the 16 patients taking omeprazole during the 6-month treatment and subsequent follow-up [9]. However, only one patient had relapse of reflux esophagitis (grade II according to the Hetzel et al. classification) in the placebo arm, and there were no relapses in the ranitidine arm, suggesting that the natural propensity to relapse was inherently low in this pediatric population. It is notable that this study specifically excluded children with chronic conditions such as cerebral palsy, repaired esophageal atresia, neurological impairment, or repaired tracheoesophageal fistula (TOF) [64]. In the first of two retrospective studies [97], regular endoscopic assessments during a mean follow-up of 4.4 years showed that healed reflux esophagitis was maintained in all 15 children while taking omeprazole (doses used during the follow-up period were not specified; reflux esophagitis was defined as at least grade II according to the Hetzel et al. classification). The second study [98] was a retrospective

chart review of 31 children who received >6 months of omeprazole maintenance therapy for reflux esophagitis. Endoscopy was repeated in these patients until reflux esophagitis was healed and then annually thereafter. In all of the patients, reflux esophagitis significantly improved (details not specified), as did their reflux symptoms. These improvements were sustained during omeprazole maintenance treatment (mean dose 1.5 mg/kg/day, range 0.6–3.3 mg/kg/day) during a mean follow-up of 31 months (range 6–90 months). In both of studies, the majority of patients had chronic conditions such as cerebral palsy, repaired esophageal atresia, neurological impairment, or repaired TOF [64].

Further indirect evidence for the efficacy of PPI maintenance therapy is provided by a study that screened hospital databases for records from pediatric patients with GERD who took PPIs continuously for at least 9 months [56]. In 166 individuals (mean age at time of index 7.8 years, range 4 weeks to 17 years), the median number of symptoms declined significantly from three (interquartile range two) at first presentation to one (interquartile range one) on the last encounter. The median follow-up between presentation and last encounter was 3 years, during which PPIs (omeprazole [85 %], lansoprazole [4.2 %], omeprazole, and þ lansoprazole [6 %]) were used for a median period of 2.75 years, omeprazole at a median dose of 1.1 mg/kg/day, and lansoprazole at a median dose of 1.4 mg/kg/day. All of the patients who were followed-up underwent esophageal endoscopy at some point during the study period. Although reflux esophagitis (classification system not reported) was endoscopically confirmed in 81 (48.8 %) of these 166 patients, specific details for rates of healing or relapse of reflux esophagitis were not given. Seventy-nine percent of the patients had comorbid conditions such as neurological disorders, esophageal atresia or TOF, or chronic lung disorders [64].

In summary, few studies have documented the efficacy of maintenance treatment with PPIs in pediatric patients after healing of reflux esophagitis. The small number of studies identified in a recent review [64] suggested that PPI maintenance therapy in pediatric patients aged 1–17 years is associated with low relapse rates for reflux esophagitis (0–25 %) and reflux symptoms (0–34 %) for follow-up durations of 6–90 months. Indeed, no relapses of reflux esophagitis in 6-month to 4.4-year follow-up were reported during PPI treatment in three of the five studies reviewed. In the remaining two studies, relapse of reflux esophagitis (14 % and 25 %) and reflux symptoms (14 % and 34 %) (after 3- and 21-month follow-up) occurred only when half the healing dose was used but resolved again in most patients when the healing dose or higher was given. The relapse rates observed for reflux symptoms and reflux esophagitis in patients receiving suboptimal PPI doses suggest that long-term therapy at the full maintenance dose is needed in some children.

In a recent open-labeled, uncontrolled, prospective study [74] to evaluate the effects of three treatment strategies after 8 weeks of lansoprazole therapy for GERD in children, 37 erosive reflux disease (ERD) and 20 NERD patients were divided into three groups by symptom assessment at 8 weeks: (1) observation without treatment in the "symptoms-resolved" group, (2) "on-demand" treatment for an additional 16 weeks in the "symptoms-attenuated" group, and (3) continuous treatment in the "symptoms-persistent" group. For ERD, six (100 %) out of six patients in the "symptoms-resolved" group remained improved at weeks 16 and 24. Sixteen (72.7 %) out of 22 patients in the "symptoms-attenuated" group had improvement of symptoms at 16 weeks and 18 (81.8 %) patients at 24 weeks. Six (66.7 %) out of nine patients in the "symptoms-persistent" group remained improved at weeks 16 and 24. For NERD, seven (100 %) out of seven patients in the "symptoms-resolved" group remained improved at weeks 16 and 24. Eight (80.0 %) out of ten patients in the "symptoms-attenuated" group remained improved at week 16 and 10 (100.0 %) patients at week 24. None out of three patients in the "symptoms-persistent" group remained improved at weeks 16 and 24. In conclusion the selection of each alternative for long-term management according to the results of the assessment of symptoms at week 8 was useful and well tolerated. "On-demand" therapy was equally effective. The 16-week therapy had the same efficacy as

the 24-week therapy with regard to long-term lansoprazole treatment [74].

A recent systematic literature analysis [64] identified four studies [9, 23, 28] that evaluated *relapse of reflux esophagitis and/or reflux symptoms after stopping PPI therapy*. Reflux symptoms recurred in 18–76 % of patients across all four studies [64]. In studies where patients stopped PPI treatment after healing, rates of relapse of reflux esophagitis and reflux symptoms were variable: 2.2 % and 30 % [9, 28] for reflux esophagitis and 18–76 % for symptoms [9, 28]. (The duration of follow-up was 2 and 3 months in two studies and not specified in the other two studies.) In the four studies that assessed the safety of PPI maintenance therapy, adverse events were infrequent and of low severity [64]. In the study by Hassall et al. [56], PPIs were used in 86 patients (52 %) for 0.75 to 3 years and 80 patients (48 %) for 3–11 years; omeprazole was the most commonly prescribed PPI (91 %), followed by lansoprazole (10 %). Only six adverse events potentially related to PPI use (nausea, vomiting, diarrhea, rash, agitation, and irritability) were recorded among four children, three of whom were taking omeprazole. A subgroup of 62 patients in this study had > one set of gastric biopsies during routine clinical care. Assessment of these biopsies showed that children did not develop atrophic gastritis, carcinoid tumors, or clinically significant enterochromaffin cell-like hyperplasia [94].

In a retrospective study of 113 children receiving continuous lansoprazole or omeprazole (mean ages, 6.7 and 8.3 years, respectively) for at least 1 year (64 % lansoprazole [mean dose, 1.42 mg/kg/day], 22 % omeprazole [mean dose, 1.15 mg kg/day]), adverse events were reported by 12 % of children, with diarrhea (5 %) and constipation (4 %) being the most common [114]. No clinically apparent adverse events were observed in the study by Pashankar et al. [97]. In addition, in the study from Hassall [55], omeprazole was well tolerated and no serious adverse events could be attributed to the drug. Thus, the evidence indicates that maintenance therapy, when required, should provide a favorable benefit-to-risk ratio [64].

The guidelines [125] attribute the recurrence of symptoms after repeated trials of PPI withdrawal to chronic-relapsing GERD and recommend long-term PPI therapy or surgery as therapeutic options in such situations. The low relapse rates observed by Boccia et al. [9] suggest that reflux esophagitis in pediatric patients who do not have certain chronic comorbidities may require only PPI healing treatment and not maintenance therapy. Conversely, patients with reflux esophagitis who have underlying predisposing disorders are likely to need long-term PPI maintenance treatment. This view is supported by the study of Hassall et al. that found 131 (79 %) of 166 patients (mean age 7.8 years) taking PPIs for longer than 9 months had these underlying conditions [56].

In summary, pediatric patients with GERD and certain chronic comorbidities (such as neurological impairment, repaired esophageal atresia, or TOF.) appear to have the greatest need of maintenance PPI treatment after healing of reflux esophagitis [64]. In patients requiring maintenance therapy, PPIs appear to be well tolerated and effective in maintaining remission of reflux esophagitis and reflux symptoms [64].

Barrett's Esophagus (BE)

The management of nondysplastic BE is the same as that of erosive esophagitis, that is, long-term PPI or antireflux surgery [54, 126]. BE per se is not an indication for antireflux surgery. In BE, symptoms are often a poor guide to adequacy of treatment, and some advocate more aggressive acid suppression, based on esophageal pH monitoring [126]. Although it is unclear whether progression of dysplasia is slowed by acid control, higher doses of PPI may be considered in BE than in esophagitis without metaplasia [104].

Dysphagia, Odynophagia, and Food Refusal

In patients with dysphagia, odynophagia, and food refusal, therapy with acid suppression without earlier evaluation to rule out other conditions

(such as barium esophagogram and upper endoscopy) is not recommended [125].

Apnea or Apparent Life-Threatening Event

In the majority of infants with apnea or apparent life-threatening events (ALTEs), GER is not the cause. In the uncommon circumstance in which a relation between symptoms and GER is suspected or in those with recurrent symptoms, MII/pH esophageal monitoring in combination with polysomnographic recording and precise, synchronous symptom recording may aid in establishing cause and effect [125] and the need for long-term medical or surgical antireflux therapy.

Reactive Airway Disease

In patients with *asthma* who also have heartburn, reflux may be a contributing factor to the asthma. Despite a high frequency of abnormal reflux studies in patients with asthma who do not have heartburn, there is no strong evidence to support empiric PPI therapy in unselected pediatric patients with wheezing or asthma. Only three groups—those with heartburn, those with nocturnal asthma symptoms, and those with steroid-dependent difficult-to-control asthma—may derive some benefit from long-term medical or surgical antireflux therapy [125].

Finding abnormal esophageal pH exposure by esophageal pH monitoring, with or without impedance, before considering a trial of long-term PPI therapy or surgery may be useful, although the predictive value of these studies for this purpose has not been established. The relative efficacy of medical versus surgical therapy for GERD in children with asthma is unknown. Although adult studies show only limited, if any, benefit from PPI or surgical therapy, it is possible that selected patients with heartburn, nocturnal asthma, or steroid-dependent, difficult-to-control asthma may derive some benefit. Symptom reporting is less reliable in infants and children than in adults. Other causes of wheezing should be ruled out.

Recurrent pneumonia and interstitial lung disease may be complications of GER due to aspiration of gastric contents. No test can determine whether GER is causing recurrent pneumonia. An abnormal esophageal pH test may increase the probability that GER is a cause of recurrent pneumonia but is not a proof. A trial of nasogastric feeding may be used to exclude aspiration during swallowing as a potential cause of recurrent disease. A trial of nasojejunal therapy may help in determining whether surgical antireflux therapy is likely to be beneficial. In patients with severely impaired lung function, antireflux surgery may be necessary to prevent further pulmonary damage, despite the lack of definitive proof that GER is causative [125].

Upper Airway Symptoms

Extrapolation from adult studies suggests that PPIs will not benefit most children with upper airway symptoms [125]. Patients with chronic hoarseness, chronic cough, sinusitis, chronic otitis media, erythema, and cobblestone appearance of the larynx should not be assumed to have GERD without consideration of other potential etiologies.

A recent Cochrane systematic review [18] of 19 studies (six in infants/children and 13 in adults) has shown a lack of high-level evidence that the treatment of GERD-associated *cough* improves cough measured by subjective methods (i.e., subjective cough). Studies on milk formula thickening yielded inconsistent results, and the single randomized controlled trial (RCT) on PPI in pediatrics (162 children) found no significant difference between groups for cough as primary outcome (95 % CI of number needed to treat for benefit (NNT-B) of 11 to number needed to treat for harm (NNT-H) of eight) or other cough outcomes. Importantly, serious adverse events, particularly lower respiratory tract infections, occurred significantly more frequently in the lansoprazole group compared with the placebo group; the NNT-H after 4 weeks was 11 (95 % CI, 3–232). In adults, there was no significant effect in the pooled analysis, and the beneficial

effect was seen only in the subgroup analysis. The OR for cough resolution pooled from four adult studies was not statistically significant (NNT-B of 4 to NNT-H of 90). This review also highlights the large placebo and time–period effect of treatment for chronic cough.

Because GERD and otitis media with effusion (*OME*) are two of the most prevalent diseases in young children, a number of investigators have taken preliminary steps to demonstrate a causative link between the diseases. Of particular interest has been the presence of gastric enzymes in the middle ear space. Studies on rats with repeated middle ear exposure to pepsin have demonstrated impaired eustachian tube function [60] as well as impaired mucociliary clearance of middle ear contents [128]. In a study by Tasker et al. [111], middle ear effusions were sampled from 54 children aged 2–8 years who underwent myringotomy. More than 80 % of the children were found to have pepsin concentrations of up to 1,000-fold greater than serum levels, suggesting a contributory role of GERD in OME [111]. Subsequent studies of middle ear fluid in children aged 1–7 years with RAOM (define) or OME demonstrated the presence of pepsin in 73–77 % of effusions [22, 59, 77]. One study of 31 children with OME showed middle ear pepsin/pepsinogen to be present in concentrations up to 231 times higher than serum levels from the same children [1]. A correlation was also identified between the concentration of the enzyme and the number of reflux episodes using 24-h pH-probe monitoring [1]. A recent prospective study [93] found that pepsin was detectable in the middle ear cleft of 20 % of 509 patients with OME undergoing tympanostomy, compared with 1.4 % of controls undergoing cochlear implantation.

Helicobacter pylori, which is a known pathogen for several inflammatory gastric disorders, also has been postulated as a factor in the development of OM (otitis media). In a study by Yilmaz et al. of 18 children with OME [131], *H. pylori* was identified by reverse transcription–polymerase chain reaction in 67 % of middle ear effusions. Additional research is necessary to determine the significance of these findings.

Although basic science studies suggest that GERD has a role in the pathogenesis of OME, there have been few clinical studies evaluating GERD in patients with OM. In a recent prospective study of the QOL effect of antireflux therapy on otologic disease [85], 37 young children (6 months to 7 years) with OM with effusion or recurrent acute OM and GERD have improved quality of life following treatment with antireflux therapy. Mean (SD) change scores for OM six-item quality-of-life survey were 1.6 (1.1) at second visit and 1.5 (1.1) at third visit ($P = 001$ and $P = 0.004$, respectively). Hearing loss demonstrated on audiometric testing was significantly improved following therapy, as were laryngeal findings of reflux on fiber-optic laryngoscopy (FOL), although a validated scale for assessment is lacking. The authors conclude that reduction of GER may play a role in the prevention of OM and avoidance of tympanostomy, although additional high-quality clinical trials are warranted.

Dental Erosions

An association between GERD and dental erosions has been established. The severity of dental erosions seems to be correlated with the presence of GERD symptoms and, in adults, with the severity of proximal esophageal or oral exposure to an acidic pH. Young children and children with neurological impairment appear to be at the greatest risk [125].

Dystonic Head Posturing (Sandifer Syndrome)

Sandifer syndrome (spasmodic torsional dystonia with arching of the back and opisthotonic posturing, mainly involving the neck and back) is an uncommon but specific manifestation of GERD. It resolves with antireflux treatment [125].

Group at High Risk for GERD

Certain conditions are predisposed to severe, chronic GERD. These include neurological

impairment, obesity, repaired esophageal atresia or other congenital esophageal disease, cystic fibrosis, hiatal hernia, repaired achalasia, lung transplantation, and a family history of GERD, BE, or esophageal adenocarcinoma.

Although many premature infants are diagnosed with GERD because of nonspecific symptoms of feeding intolerance, apnea spells, feeding refusal, and pain behavior, there are no controlled data that confirm reflux as a cause. Although reflux may be more common in infants with bronchopulmonary dysplasia, there is no evidence that antireflux therapy affects the clinical course or outcome of this condition.

Pediatric patients with GERD and certain chronic comorbidities (such as neurological impairment, repaired esophageal atresia, or TOF.) appear to have the greatest need of maintenance PPI treatment after healing of reflux esophagitis [64].

Helicobacter pylori Infection

In pediatric efficacy studies for the management of *H. pylori* eradication in children, the most commonly tested regimen has contained a combination of PPI, clarithromycin, and amoxicillin, followed by triple therapies containing PPI, clarithromycin, and nitroimidazoles [19]. Thus, PPIs are an integral part of triple therapy for *H. pylori* eradication in children with gastroduodenal disease. Almost all published efficacy studies in pediatric patients have been performed with omeprazole and lansoprazole used in combination therapies for the first-line treatment of *H. pylori* eradication.

PPIs have been shown to exert a specific antibacterial activity against *H. pylori* in vitro [110]. However, in vitro antimicrobial activity does not necessarily indicate that the drug will demonstrate an effect in vivo. In vivo, PPI alone suppresses *H. pylori* growth but does not lead to eradication of the organism [69, 127]. The main reason to use PPIs in *H. pylori* eradication regimens is to achieve a favorable intragastric pH window that facilitates the antimicrobial effects of antibiotics [101]. Acid-sensitive antibiotics such as amoxicillin and clarithromycin require rapidly acting PPIs to create an optimum pH window for optimum antibacterial effect [101]. Increasing intragastric pH has been shown to achieve higher *H. pylori* eradication rates as well as ulcer healing rates by stabilizing acid-labile antibiotics, which increases the concentration of antibiotics in gastric juice [30]. In addition, the synergistic effect of PPIs and antibiotics in vivo is due to the fact that PPIs not only increase intragastric pH but reduce gastric juice volume [46, 124]. Goddard and Spiller [47] showed that omeprazole decreases gastric juice viscosity by its effect on pH, implying a reduction in the mucus barrier function of the stomach. Both of these actions will improve local drug delivery to the gastric mucosa and surface epithelial cells that serve as the habitat for *H. pylori* colonization of the stomach. Pediatric studies suggest that PPIs are safe and effective drugs for use in the eradication of *H. pylori* infection and management of peptic acid-related disease.

Critically Ill Children

PPIs can be used intravenously in critically ill children for the prophylaxis and treatment of gastrointestinal hemorrhage, although there is still little experience with this. In critical patients, acid secretion is induced by gastrin or histamine released by stress. This acid secretion injures the gastric mucous producing digestive bleeding. Morbidity and mortality are increased in critically ill adult and pediatric patients who are at high risk of gastrointestinal hemorrhage. Mechanical ventilation for more than 48 h, coagulation disorders, shock, neurosurgery, respiratory failure, and sepsis are factors that increase the risk of gastrointestinal hemorrhage [12]. Prophylaxis for gastrointestinal hemorrhage is therefore recommended in critically ill children and adults [109]. The most widely used drugs for prophylaxis are the H2 receptor antagonists and the PPIs [12, 80, 100]. Pharmacokinetics studies are necessary to analyze the most adequate omeprazole dose and interval in critically ill children.

Safety Profile

Most adverse effects occurring during the treatment with PPI are mild, self-limiting, and unrelated to patient age, the most common being diarrhea, headache, abdominal pain, nausea, constipation, and dizziness. These may resolve with decreased dose or change to a different PPI [125]. There appears to be a minimal risk of adverse effects in humans with long-term administration [99]. Acid suppression leads to increased levels of circulating gastrin in most patients [79]. Gastrin stimulates gastric acid secretion by parietal cells directly by binding to its specific receptor and indirectly through the stimulation of histamine release from enterochromaffin-like cells. Moreover, gastrin exerts a trophic effect on both parietal and enterochromaffin-like cells [81D]. When high-dose PPIs were administered to rats, hypergastrinemia, endocrine cell hyperplasia, and carcinoid tumors developed [99]. Elevated gastrin levels have been observed in patients receiving omeprazole, but serum gastrin normalized once the drug was discontinued [99]. In addition, benign gastric changes such as parietal cell hyperplasia and gastric polyps have been observed in children and adults receiving long-term PPI therapy [79, 114]. However, no carcinoid tumor formation ever has been reported in humans [79]. A recent retrospective study of children treated with PPIs for up to 11 years found only mild grades of enterochromaffin-like cell hyperplasia [56]. A high percentage of children (61 %) receiving long-term PPI continuously for up to 10.8 years (median, 2.84 years) develop minor degrees of ECL hyperplasia. This has no known clinical significance. Children on PPIs for this duration do not appear to develop atrophic gastritis or carcinoid tumors [57].

The issue of gastric adenocarcinoma in patients treated long term with PPIs has been long debated. Recently, the discussion has focused on the interaction between PPI and *H. pylori* leading to atrophic gastric as precursor of gastric adenocarcinoma [79]. In the late 1990s, Kuipers et al. [72] reported the development of atrophic gastritis in *H. pylori*-positive patients on long-term omeprazole, compared to no risk in *H. pylori*-negative patients. A recent long-term follow-up study confirmed a progression toward atrophic gastritis in *H. pylori*-positive patients on long-term omeprazole therapy [81]. Thus, the last consensus conference on *H. pylori* infection recommended *H. pylori* eradication in patients requiring long-term maintenance treatment with PPI [82].

In a recent study [94], infants treated with PPI had a significantly higher rate of all adverse effects compared with the placebo group. Lower respiratory tract infections were the most frequent among these adverse effects, although the difference in respiratory tract infection rate between treated and placebo groups did not achieve statistical significance. It has been repeatedly reported that the suppression of gastric acidity predisposes to infection by a variety of pathogens, but only recently has the increased risk of infection induced by gastric acidity inhibitors (GAIs) been investigated systematically at clinical and laboratory level [84]. Gastric juice consists of HCl and pepsin and can kill bacteria within 15 min when the pH is less than 3.0. If the pH is raised above 4.0, a state defined as hypochlorhydria, bacterial overgrowth and infections are more common [31]. Berni Canani et al. [16] reviewed recent clinical studies performed in adults, children, and neonates exploring the possible association of gastric acidity inhibitors' use with intestinal infections. Many studies and systematic reviews demonstrate an increased risk of bacterial infection in adults taking acid suppressors [14, 34, 37, 42, 76]. Little evidence is derived from the pediatric population. A recent case-control study of risk factors for *Salmonella enteritidis* in the Netherlands showed an increased risk of gastroenteritis induced by these pathogens in children taking GAIs (OR 3.6, range 1.9–6.9) [33]. A prospective study performed in pediatric patients showed that the use of GAIs is associated with an increased risk of acute gastroenteritis and community-acquired pneumonia in GERD-affected children [6]. The authors obtained data on 186 participants from four pediatric gastroenterology centers: 95 healthy controls and 91 GAI users (47 on ranitidine

and 44 on omeprazole). The two groups were comparable for age, sex, weight, length, and incidence of acute gastroenteritis and pneumonia in the 4 months prior to enrollment. Rate of acute gastroenteritis and community-acquired pneumonia was significantly increased in patients treated with GAIs compared with healthy controls (acute gastroenteritis, 47 vs. 20 %, $P = 0.001$; pneumonia, 12 vs. 2 %, $P = 0.03$) during the 4-month follow-up period. In the GAI-treated group, the rate of acute gastroenteritis (20 vs. 47 %, $P < 0.0001$) and community-acquired pneumonia (3 vs. 12 %, $P = 0.02$) was increased when comparing the rates 4 months before and after the enrollment. No differences in acute gastroenteritis and pneumonia incidence were observed between ranitidine and omeprazole users in the previous 4 months and during the follow-up period. On the contrary, in healthy controls, the incidence of acute gastroenteritis and pneumonia remained stable. It is interesting to note that in this study authors observed an increased incidence of intestinal and respiratory infections in otherwise healthy children taking GAIs for GERD treatment. On the contrary, the majority of the previous data showed that the patients most at risk for pneumonia were those with significant comorbidities such as diabetes or immunodeficiency, and this points to the importance of gastric acidity suppression as a major risk factor for infections. The effect on infection susceptibility seems to be sustained even after the end of therapy. Authors observed a similar incidence of acute gastroenteritis and pneumonia during the use of GAI drugs and in the 2 months following stopping their use as observed previously in adult patients [121]. How long this effect can last remains to be defined in future studies. Children exposed to PPIs therapy seem to be at higher risk for the development of *Clostridium difficile*-associated disease [119]. The use of PPI was significantly higher in *C. difficile*-positive group compared with *C. difficile*-negative group (odds ratio [OR] = 4.5; 95 % confidence interval [CI] = 1.4–14.4).

It has been recently reported in a retrospective study that at least 30 % of neonates received treatment with GAIs at the time of discharge from NICU and an additional risk of infections and necrotizing enterocolitis (NEC) in newborns treated with GAIs was observed [51]. In addition, there is no clear evidence of benefit of the use of GAIs in many clinical conditions typical of neonatal age. These observations suggest the importance of a more careful use of GAIs in these patients, in particular, if other risk factors for severe infections are present [16].

Other adverse effects have been reported in elderly patients on chronic PPI therapy, such as deficiency of vitamin B12 and increased incidence of bone fractures, but these findings have not been confirmed by recent studies [65, 114]. Based on current knowledge, routine testing for vitamin B12 deficiency is not recommended in long-term PPI users [79]. Likewise, osteoprotective prophylaxis is not recommended in patients with long-term PPI use [79]. Moreover, PPIs are considered to be the most common cause of acute interstitial nephritis in adults [13]. This adverse effect is considered to be an idiosyncratic reaction, more frequent in elderly adults. No childhood cases have been described.

Finally, physicians should be aware of emerging data suggesting a potential role for acid-suppressive medications in the pathogenesis of certain manifestations of food allergy such as eosinophilic esophagitis [86]. Recent studies have elucidated a plausible mechanism whereby antisecretory agents, by interfering with the peptic digestion of dietary proteins and by increasing mucosal permeability, might predispose to food allergy. This association warrants future epidemiological investigations.

Conclusion

Despite PPIs seeming to be well tolerated in the short term, there is insufficient evidence of effectiveness and safety in the treatment of GERD in children and adolescents. Therefore, physicians should be careful when prescribing PPI, medications that have potential adverse effects, unless there is documented disease or with careful monitoring. A proper utilization of these drugs, particularly for patients at high risk, is imperative in order to reduce deleterious effects on infection risk and to optimize cost-effectiveness ratio.

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Prokinetic Therapy

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Gigi Veereman-Wauters

Impaired esophageal motility may be the cause or the consequence of GERD and esophagitis. Transient lower esophageal sphincter relaxations lead to GERD in premature infants [1]. It remains unclear whether esophageal motor abnormalities contribute to GERD in children [2, 3], but esophageal inflammation causes altered motility [4]. Pharmacological agents that restore normal motility patterns would be highly desirable. Unfortunately, efficacious and safe prokinetic agents are currently lacking for routine clinical use.

Prokinetic agents act on the humoral or neuromotor network. In addition to the intended effects on gastrointestinal motility, these agents have central nervous system effects thus side effects. Many agents, such as bethanechol that was used 20 years ago, have more side effects than proven benefits and therefore are abandoned.

Cholinergic Agonist

Bethanechol increases lower esophageal sphincter pressure [5], but side effects such as dystonia have prohibited its use [6].

Dopamine Receptor Antagonist

Erythromycin facilitates gastric emptying. Safety profile needs to be considered, especially for cardiac effects [7]. The relationship between gastric emptying and GERD is unclear, and the effect of erythromycin on GERD is unknown.

Antidopaminergic Agents

Domperidone and metoclopramide are antidopaminergic agents that facilitate gastric emptying.

Metoclopramide has largely been abandoned because of disturbing neurological side effects such as irritability and dystonia in addition to a questionable effect on GERD [8].

Domperidone is used as antiemetic and has no proven effect on GERD. A study in newborns showed an unexpected increase in reflux episodes [9]. Domperidone occasionally causes extrapyramidal central nervous system side effects and rarely produces QTc prolongation on electrocardiogram.

Serotonergic Agent

Cisapride facilitates the release of acetylcholine at synapses in the myenteric plexus, thereby improving overall gastrointestinal peristalsis. This well-known prokinetic agent has been

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Table 90.1 Dosages for prokinetics

Metoclopramide 0.1 mg/kg/dose qid/AC
Cisapride[a] 0.2 mg/kg/dose qid/AC
Erythromycin 3–5 mg/kg/dose tid-qid/AC
Domperidone pediatric doses not defined
Bethanechol 0.1–0.3 mg/kg/dose tid-qid/AC

AC ante cibum
[a]Restricted or unavailable

withdrawn from the markets because of the risk for prolongation of the QTc interval on electrocardiogram and lack of well-demonstrated efficacy on GERD [10, 11].

Gamma-Aminobutyric-Acid Receptor Agonist

Baclofen inhibits transient lower esophageal sphincter relaxations. A reduction of emesis and improvement of reflux parameters were demonstrated in children with cerebral palsy [12]. Likewise GERD and gastric emptying improved in otherwise healthy children [13]. The safety profile of this drug again precludes routine use: dyspeptic symptoms, drowsiness, dizziness, fatigue, and seizures (Table 90.1).

According to the most recent guidelines, there currently is insufficient evidence to justify the routine use of domperidone, baclofen, cisapride, metoclopramide, erythromycin, or bethanechol for GERD [14].

It is hoped that new compounds will be developed and proposed for pediatric clinical trials.

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Part XVI

Surgical Therapies

Gastroesophageal Reflux: Issues from a Surgeon's Perspective

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Ma Pilar Abad Calvo and J. Boix Ochoa

Abbreviations

DGE	Delayed gastric emptying
GER	Gastroesophageal reflux
GERD	Gastroesophageal reflux disease
HPZ	High-pressure zone
LES	Lower esophageal sphincter
MAO	Maximal acid output
MII	Multichannel intraluminal impedance
NI	Neurological impairment
PPIs	Proton pump inhibitors
RI	Percentage of time with pH less than 4.0, reflux index
TLERs	Transient lower esophageal sphincter relaxations

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Defining Gastroesophageal Reflux

Gastroesophageal reflux GER is defined as a return of gastric contents into the esophagus with or without regurgitation and vomiting. GER is a normal physiologic process occurring several times per day in healthy infants, children, and adults [309]. Most episodes of GER last less than 3 min and occur in the postprandial period, with few or no symptoms [267].

It is common for infants to have recurrent problems with "spitting up" or "vomiting" during the first year of life. The severity of symptoms varies from an occasional burp to persistent emesis. Evaluation of most of these infants reveals no definable anatomic, metabolic, infectious, or neurologic etiology. Gastroesophageal reflux (GER) should cause concern only when associated with additional problems such as abnormal persistence, growth retardation, and respiratory symptoms. The spectrum of clinical symptoms in pathological GER is wide and complications are at times severe so that recognition of possible pathological vomiting followed by appropriate diagnostic makes therapeutic steps essential. About 60–65 % of such infants without treatment are essentially free of symptoms and in good health by 2 years of age. The remaining have persistent and significant symptoms until at least 4 years of age, and about 4 % of the total group develop esophageal strictures. Carré estimated a mortality of 5 % in those without strictures, usually from inanition or infection [59].

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Factors Related to GER

Anatomy and Genetics

The esophagus develops from the primitive foregut which lies immediately caudal to the pharynx. As the neck and trachea develop, the esophagus lengthens rapidly from above downward, traveling through the neck, the posterior mediastinum, and the esophageal hiatus to end in the cardia of the stomach. Between the fourth and seventh weeks of gestation, the stomach moves caudally, and failure of this process results in a short esophagus [327] and a partially thoracic stomach that was described by Carré.

The length of the esophagus varies depending on age, sex, and individual habitus. The tubercle of the cricoid cartilage is the single constant landmark of the upper esophageal opening. We believe that division into cervical, upper, middle, and lower thoracic and abdominal segments is adequate. Talking about GER, the lower thoracic and abdominal segments are the most important, since the antireflux mechanism, which prevents return of gastric material into the esophagus, depends on their anatomy and physiology (Fig. 91.1).

The formation of the gastroesophageal junction results from a complex but coordinated development of the esophagus, diaphragm, and stomach together with the autonomic nerve innervation and the blood supply of these viscera [172]. Failure of this process of development and maturation results in structural defects and functional abnormalities that can lead to GER.

Lately, attention has focused on the possibility that gastroesophageal reflux disease may have a genetic basis. A specific locus associated with pediatric GERD has been identified on chromosome 13. The identification of the molecular mechanisms underlying familial pediatric GERD will have important consequences both for our understanding of the pathophysiology of this common and costly disorder and for our ability to more accurately target treatments at those mechanisms [139, 140, 225].

Pathophysiology

The pathophysiology of gastroesophageal reflux disease involves contact of the esophageal epithelium with acid/pepsin in the refluxate. For this contact to occur with sufficient duration, there must be a combination of defects in antireflux and luminal clearance mechanisms for acid/pepsin to overwhelm an intact epithelium; otherwise, defects within the epithelium develop that subsequently enable normal acid contact times to become damaging to the epithelium (Table 91.1). Three major tiers of defense serve to limit the

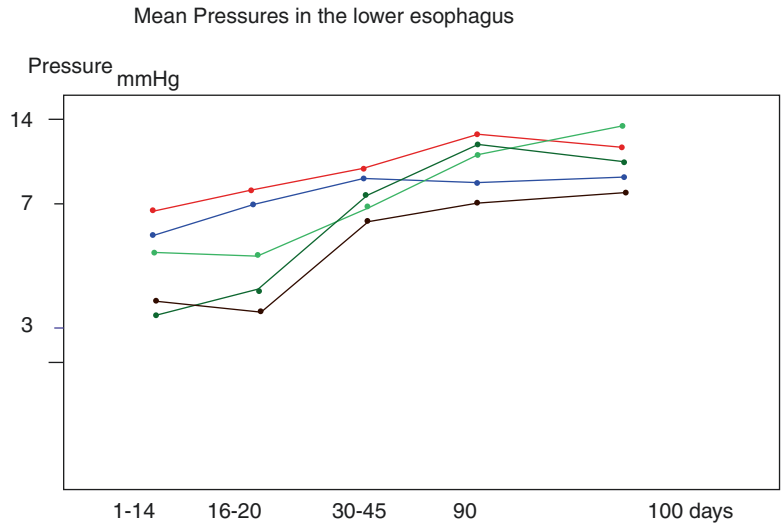


Fig. 91.1 Mean pressures in the lower esophagus, independent of perinatal factors, converge at 5–9 weeks to their effective maturation. The length of the abdominal portion of the esophagus is the decisive factor in the antireflux mechanism. Boix-Ochoa and Canals [32]

Table 91.1 Pathophysiological mechanisms of GER

LES dysfunction: defective basal LES pressure
Intra-abdominal esophagus: anatomical anomalies
Loss of extrinsic support by the crural diaphragm: TLESR
Delayed gastric emptying

degree of GER and to minimize the risk of reflux-induced injury to the esophagus.

The first line of defense is the "antireflux barrier," consisting of the lower esophageal sphincter (LES), and the diaphragmatic pinch cock and angle of His; this barrier serves to limit the frequency and volume of refluxed gastric contents. When this line of defenses fails, the second "esophageal clearance" assumes greater importance, to limit the duration of contact between luminal contents and esophageal epithelium. Gravity and esophageal peristalsis serve to remove volume from the esophageal lumen, while salivary and esophageal secretions (the latter form esophageal submucosal glands) serve to neutralize acid.

The third line of defense, "tissue or esophageal mucosal resistance," comes into play when esophageal clearance is defective or not operative (e.g., motility disorders, sleep).

The Antireflux Barrier

Lower Esophageal Sphincter: Dysfunction

In 1956, as a result of the development of esophageal manometry, a high-pressure zone (HPZ) near the esophagogastric junction was described. A sphincter muscle in the lower esophagus was proposed as the mechanism for maintaining this pressure [111]. Meticulous dissections of the esophagus revealed an oblique gastroesophageal ring caused by a meager increase in muscle mass [181]. The well-defined HPZ exists in the lower esophagus, referred to as the LES.

The esophageal peristalsis normally begins in the pharynx, progressing down the esophagus and producing, at the appropriate time, relaxation of the LES [47]. This relaxation is brief, but the mechanism results in effective and rapid passage of ingested food and saliva from the pharynx to the stomach [13]. Presumably, afferent and efferent vagal neural pathways controlled by brain stem nuclei mediate this sequence of events [199]. The cause of the HPZ remains conjectural, but it is unlikely to be solely the result of a true muscle sphincter [181]. Patients who have had surgical removal of the distal esophagus (esophagogastrectomy) have, in manometric studies, an HPZ at the thoracoabdominal junction that relaxes on swallowing and increases with a rise in intra-abdominal pressure [173].

Intra-abdominal Esophagus: Anatomical Anomalies

The presence of an intra-abdominal esophagus is vital to the antireflux barrier [40, 228] and is the key to the whole system [31, 85]. The determining factor is the length of the esophagus exposed to intra-abdominal pressure [150, 320, 326]. The greater the length of the intra-abdominal esophagus, the more esophageal valve becomes [293].

The segment of intra-abdominal esophagus, which is a soft tube, is collapsed when intra-abdominal pressure increases. The diameter of the esophagus is one fifth than that of the stomach. Hence, according to Laplace's law, the pressure in the esophagus to enable it to act as a closing valve should increase by only one fifth of the pressure of the stomach. A sufficient segment (>2 cm) of abdominal esophagus is the best guarantee of an effective antireflux choice of surgical procedure [40]. In newborns and older infants, we have demonstrated that the pars abdominalis is the cornerstone of the antireflux barrier [32].

Pinch-Cock Action

The esophagus crosses the diaphragm at the hiatus, a sling-shaped orifice formed by the right crux of the diaphragm. The anatomical disposition of this diaphragmatic sling pulls the esophagus to the right and downward, narrowing its lumen during deep inspiration [201]. As the esophagus passes through the hiatus, it is surrounded by the phrenoesophageal membrane. The insertion of the phrenoesophageal membrane [6, 69, 86] marks the level at which the esophagus changes from an intrathoracic to an intra-abdominal structure [39, 190, 310]. This pinch-

cock action of the diaphragm [222] can easily be observed during endoscopy and functions to increase the LES pressures [7–200] through the interaction of the axial movement of the LES and the diaphragmatic contraction [23, 43].

Angle of His

The angle of His is formed by the esophagus at its union with the stomach. In children with an abdominal esophagus of normal length, the angle of His is acute which creates a double antireflux effect. When the patient attempts to vomit, more gastric contents strike the fundus than escape through the esophagus. Pressure of the contents striking the fundus narrows the angle and compresses the esophagus. However, if the angle is obtuse (e.g., as occurs from a short esophagus, hiatal hernia, or esophageal atresia), the upper stomach is converted into a funnel and the fluids are directed into the esophagus. The concept of the angle of His must be kept in mind when considering the most appropriate surgical technique to correct reflux in children [33].

Mucosal Rosette

In the presence of a normal angle of His, there is a convoluted fold of mucosa with a rosette-like configuration at the gastroesophageal junction. With increases in intragastric pressure or with negative pressure in the thoracic esophagus, these mucosal folds squeeze together and act as a weak antireflux valve [240].

Crural Diaphragm: Loss of Extrinsic Support

The crural diaphragm constitutes the external mechanism of the LES [83]. The phrenoesophageal ligament anchors the distal esophagus to the crural diaphragm [43]; therefore contraction of the crural diaphragm exerts with the sling fibers of the right crus a pinch-cock-like action on the LES [173, 271]. Changes in the LES pressures are also related to contractions of the crural diaphragm. Normally these contractions are linked with respiration. Each inspiration increases the pressure [191–257]. The pressure gradient between the esophagus and the stomach is constantly changing and the esophagogastric junction pressure must constantly adapt to counteract these changes. This adaptive response is mediated through contraction of either the intrinsic esophageal sphincter or the crural diaphragm. The rapid contraction of the crural diaphragm, a fraction of a second earlier than the costal diaphragm, counteracts this increase in gastric pressure maintaining the antireflux barrier [191, 271].

Which minimum anatomical conditions and physiological pressures we have to achieve to ensure the antireflux barrier? Two pillars emerge as cornerstones for maintaining competence: a critical sphincter pressure to counteract increases in intragastric pressure and sufficient length of intra-abdominal esophagus to counter increases in intra-abdominal pressure. If either is reduced, the other one must increase if competency is to be maintained [7, 40]. A hiatal hernia or a short esophagus leading to an incompetent intra-abdominal esophagus, an obtuse angle of His, a weak mucosal choke, and reduction of the effective overall length of the LES weakens these cornerstones and permits GER [205]. Thus, a major goal when surgical therapy is indicated is always to create a sufficiently long intra-abdominal esophagus. We have been able to demonstrate in our pediatric patients that this length varies between 1.5 and 2 cm.

The competency of the antireflux barrier, LES, depends on [40, 331] a sphincter pressure above the 2.5 percentile (>6 mmHg), an intra-abdominal esophageal length in at least the 5th percentile (>1 cm), and an overall length of the LES above the 2.5 percentile (>2 cm) [129].

The reflux occurs when opening pressures exceed closing pressures, which is not always due to the incompetence of the antireflux barrier and may be due to a pathological increase of opening pressures [6, 87–89]. We have always said that a door will not open if nobody pushes it; therefore, it would be illogical to surgically reinforce normal mechanisms without paying attention to abnormal forces that are pushing [37]. Lately this traditional view held for many years has changed abruptly. The majority of cases with reflux is no more a problem of a weak antibarrier reflux or a pathological increase in opening pressures that opens a door. The problem now

is that the door opens automatically in the middle of normal parameters [246] the so-called transient lower esophageal sphincter relaxation" (TLESR) [304].

Opening Pressures

The retention and dilatation of the stomach creates a distracting force producing an increase in the tension of the gastric wall in the direction of the muscle fibers extending from the esophagus. This reduces sphincter length until the sphincter opens. The damaging effect of increased diameter could only be reversed by increasing the sphincter length, but gastric distension logically shortens the overall length of the intra-abdominal segment taking away the patient's last chance against reflux [169].

Delayed Gastric Emptying

In a study of the patterns of reflux, patients who had reflux in the upright position tended to have their reflux episodes within 2 h after a meal [84]. A radionuclide gastric emptying study in one of these patients showed significant DGE. A follow-up on this observation studied patients with symptoms suggestive of GER [185]. Gastric emptying was normal in those with reflux but without esophagitis and in the controls, but those with esophagitis had significant DGE. The techniques and clinical usefulness of radionuclides in the study of gastric emptying revealed that studies with radionuclide techniques showed DGE in more than 40 % of patients with GER [137]. Gastric emptying in patients with reflux was studied before and after fundoplications [188]. With both liquid and solid meals, gastric emptying was significantly more rapid 6 months after fundoplication than preoperatively.

Studies have shown DGE of water in children with GER [97], but other studies have found no significant differences in gastric emptying (using apple juice as the vehicle for the radionuclide marker) between patients with and without reflux [156]. In a separate study, the latter investigators focused on the relationship of gastric emptying to retching symptoms occurring following antireflux surgery [157]. This proved complex.

Experience with a large group of children treated surgically for GER has advocated pyloroplasty in conjunction with fundoplication when preoperative DGE is found [108]. In a review of 420 children treated surgically, the conclusion was that reflux and DGE were often a part of a more generalized intestinal motor disorder. Some 50 % of children with symptoms of reflux also have DGE, and this percentage is much higher in those with severe mental impairment. Again, the high risk of DGE with refluxing children who have serious mental retardation is emphasized [105].

Evaluation of gastric emptying in 99 children with GER revealed 28 with DGE [233]. Of the patients with DGE, 75 % were neurologically impaired (NI).

Some reported findings in NI children with GER are totally at variance to the above [193]. Another retrospective study in refluxing children with neurologic disorders confirmed that pyloroplasty was of little benefit [57].

Because there is no way to predict which patients with normal gastric emptying preoperatively would show DGE postoperatively and because the large majority of those with DGE preoperatively demonstrate normal gastric emptying afterward, a gastric drainage operation at the time of the antireflux procedure is not felt to be warranted [51].

Clearly, this issue remains unsettled. Because an antireflux operation often results in more rapid gastric emptying and because many children with DGE revert to normal gastric emptying patterns, perhaps it is reasonable not perform a gastric drainage procedure before the antireflux operation.

Total gastric emptying is delayed in 10–33 % of adult patients with GERD. Patients with GERD might have exaggerated postprandial fundus relaxation with retention of food and triggering of TLERs. Using simultaneous gastric emptying and esophageal pH impedance, some studies show that the slower the emptying, the higher the pH and proximal extent of the refluxate [94].

Breaking the Barrier

Why does GER occurred? Until the 1980s, the fault was believed to be low basal pressures in the

LES. On average, the basal pressure of the LES is lower in refluxing patients than in normal individuals, but there is a great deal of overlap. Surprisingly, GER is not uncommonly associated with a hypertensive LES [162]. In a study of asymptomatic people using combined continuous recordings of the esophageal pH and pressure, reflux occurred during transient drops in pressure (sphincter relaxations) not coincident with swallowing. These inappropriate TLESRs occurred spontaneously or immediately following the brief period of normal relaxation stimulated by swallowing (Fig. 91.1). Most of the episodes of reflux occurred within 3 h after eating. Extending these studies to patients with symptomatic GER, more than 80 % of reflux episodes occurred during periods of TLESR. Absent basal lower esophageal pressure became a significant mechanism with increasingly severe esophagitis and was associated with 23 % of GER episodes in the study group with most severe esophagitis.

These same monitoring techniques were used to study 29 children (ages 5 days to 2 years) with symptoms suggesting reflux [321]. Transient increases in intra-abdominal pressure (spontaneous or induced by stress) accounted for 54 % of reflux episodes, and TLESR accounted for 34 %. In a later study of another group of children with reflux using esophageal pH and pressure monitoring, all patients without esophagitis and 77 % of those with esophagitis had reflux episodes secondary to TLESR [71]. TLESR episodes have also been found to be the predominant mechanism of GER in 94 % of premature infants [214].

Recognition of TLESR, rather than low basal LES, as the primary mechanism of reflux clearly is a major step in our understanding of this disease. In TLESR, the drop in pressure is abrupt and profound and lasts, on average, considerably longer than the normal LES pressure drops associated with swallowing. TLESR is not associated with a peristaltic wave effective in esophageal clearance; the esophageal mucosa is exposed to the noxious effects of acid gastric contents for relatively long periods. Nonetheless, the previously described parts of the antireflux barrier remain essential to the prevention of reflux, whatever the exact causative mechanism of the reflux episodes may be. Hence therapy, medical or surgical, must continue to address and correct, whenever possible, the deficiencies in the antireflux barrier mechanism.

Once the gastric juice achieves the esophagus, the damage depends on the balance between the aggressive factors and the defense mechanism (Table 91.2).

Aggressive Factors

Refluxate

Refluxated gastric juice into the esophagus may damage the epithelium through the presence of hydrochloric acid (HCl), pepsin, bile salts (conjugated and deconjugated), and pancreatic enzymes (trypsin, lipase). However, when gastric pH is acidic, the major injurious factors are HCl and the acid-activated proteolytic enzyme, pepsin [294]. Deconjugated bile salts and pancreatic enzymes are ineffective at acid pH because acidity renders them either insoluble or inactive [184, 261]. Although acid/pepsin is crucial for the generation of the symptoms and signs of GERD, the rates of gastric acid and pepsin secretion in patients with GERD remain similar to those of healthy subjects. This similarity indicates that fundamentally GERD is not a disease of offensive excess but instead a disease resulting from the breakdown of one or more elements within the esophageal defensive system.

Hypersecretory state – maximal acid output (MAO): the number concentration of hydrogen

Table 91.2 Mechanisms of the esophagitis

Frequency of GER
Duration of refluxate contact
Gravity
Peristaltic clearance
Salivary neutralization
Reflux noxiousness
Degree of hydrochloric acid exposure – hypersecretory state
Pepsin, bile acids, and trypsin
Mucosal defense
The mucosal barrier
Esophageal clearance

ions obviously is intimately related to the volume and acid of gastric secretion. We have demonstrated [30, 61] that patients with GER and elevated maximal acid output are at high risk of clinical symptomatology. However, studies in adults fail to show a direct correlation between esophageal mucosal damage and gastric hypersecretion. Further investigation in this area is required.

Defensive Factors

The hallmark of esophageal defense is represented by the luminal acid clearance mechanisms and the tissue resistance.

Esophageal Clearance

A prompt and efficient clearing of the esophagus by normal peristalsis is necessary to avoid prolonged contact between the vulnerable esophageal mucosa and gastric contents. We now know that essentially normal esophageal peristalsis occurs in healthy preterm and term babies. In both infants and children, peristaltic waves ranged from 2 to 6 s in all age groups [120, 133]. In newborns and infants (14 days to 11 months of age) with gentle regurgitation and with normal growth, peristaltic waves following swallowing were comparable with those of nonregurgitating infants in terms of duration, pressure, and progression.

A study of infants with significant reflux, however, shows a different picture. Thirty-four infants were evaluated for possible GER [11, 133]. Peristalsis was normal in those with vomiting but who were otherwise healthy. In those with failure to thrive or recurrent pulmonary disease, the amplitude of the peristaltic waves was significantly reduced and the frequency of nonperistaltic contractions was significantly increased.

Those patients with severe esophageal mucosal disease (esophagitis, stricture, Barrett's esophagus) showed impaired esophageal peristalsis that increased with the severity of the mucosal injury. Patients with reflux and esophagitis were compared with normal patients without reflux and to patients with reflux without mucosal inflammation [165]. The amplitude of peristaltic waves was lower in the esophagitis patients, and the degree of lowering increased with the severity of the esophagitis.

Esophageal peristalsis was studied in 27 infants with reflux, 3–20 months of age, by dividing the patients into those with esophagitis and those without [70]. Those with esophagitis had significantly lower amplitude of esophageal peristalsis than those with reflux alone, and nonspecific motor defects were more frequent in the first group. Most of the reflux episodes in both groups resulted from inappropriate (i.e., not associated with swallowing) relaxations of the LES, and this mechanism was more frequent in those with esophagitis. Thus, impaired esophageal peristalsis clearly is a feature of those patients with reflux complicated by esophagitis alone or with progression to stricture or Barrett's esophagus. Whether the impairment of motor function of the esophagus is a primary element of the disease or is secondary to acid reflux is not clear, but the available evidence weighs in favor of a secondary phenomenon [95].

Acid clearing, the interval while intraesophageal pH is <4 after a traditional acid reflux event, is a potential "blind spot" during pH monitoring, when reflux of acidified gastric contents may occur undetected by the pH probe. This is termed "acid rereflux." Acid rereflux comprised 61 % of acid reflux events in severe GERD. The detection of acid rereflux by impedance, manometry, and scintigraphy and the impact on acid-clearing pathophysiology will give an indication of the severity of antireflux barrier incompetence [266].

Tissue Resistance

Although clearance mechanisms minimize contact between acid and epithelium, the cumulative acid contact time, 1–2 h per day, even in healthy subjects, is significant. This observation emphasizes the necessity of having a third tier to esophageal defense against reflux injury. Tissue resistance is not a single factor but a group of dynamic mucosal structures and functions. For discussion purposes, tissue resistance can be broken down into three areas: pre-epithelial, epithelial, and postepithelial defense [219, 220].

The pre-epithelial defense is poorly developed with neither a well-defined mucous layer nor the

capacity of surface cells to secrete bicarbonate into the unstirred water layer.

The epithelial defense in the esophagus consists of structural and functional components. Structural components include the cell membranes and intercellular functional complex. These protect by limiting the rate of HCl diffusion into and between the cells. The functional components of tissue resistance include the ability of esophageal epithelial cells to buffer and to transport acid. The postepithelial defense in the esophagus is provided principally by the blood supply. Blood flow delivers oxygen, nutrients, and bicarbonate and removes H+ and CO_2. These functions provide protection by maintaining the normal tissue acid-base balance.

Traditional dogma states that GERD is a motor disease, primarily resulting from defects in the antireflux barrier. A strong case can be made, however, for GERD, at least in part, being due to an impairment in tissue resistance [220, 221].

GER: Lethal Vicious Circle

Exposure of the esophagus to gastric contents coupled with insufficiency esophageal clearance leads to esophagitis [25]. Esophagitis is not the end of the process; it is the starting point of a vicious circle. Esophagitis damages the vagal nerve fibers with consequent impaired motility both of the esophagus and stomach and leads to further esophageal damage.

As a result of the contact of the acid with the esophageal mucosa, there is an increase in the regional blood flow, increasing the local tissue content in prostaglandin E2. Prostaglandin increases the permeability of the mucosa to acid, which enhances the susceptibility of the mucosa for inflammation. Inflammation of the mucosa of the lower part of the esophagus causes an impairment of the LES (favoring GER), causing a dysmotility of the LES (favoring GER), finally causing esophagitis. The contact of acid on the esophageal mucosa causes an irritation, dysfunction, and inflammation of the local vagal nerve endings, causing an impairment of the LES and a pylorospasm. Both pylorospasm and impaired function of the LES favor GER.

Effective treatment depends on measures to block this vicious circle. Esophageal strictures [34] and Barrett's esophagus are the worst complications [63]. In Barrett's esophagus a columnar epithelium replaces the normal squamous epithelium in the lower esophagus [16, 20, 44]. Although a rare complication in children, the possibility of progression to adenocarcinoma makes early diagnosis and treatment clearly important [45–277].

Gastroesophageal Reflux Disease

GER associated with additional problems as abnormal persistence, growth retardation, and respiratory symptoms is the GERD. So GERD is present when the reflux of gastric contents causes troublesome symptoms and/or complications.

Groups at high risk for GERD are in Table 91.3. Certain conditions are predisposed to severe, chronic GERD.

Symptomatology and Complications

The complications of GER or GERD are the consequence of one of the following mechanisms: a chemical irritation of the distal esophageal mucosa, the loss of calories due to vomiting or refusal of food, and the aspiration of gastric contents or reflex mechanisms between esophageal innervation and the upper and lower airway. In some patients, more than one mechanism exists (Table 91.4).

Table 91.3 Groups at high risk for GERD

Neurological impairment
Obesity
Repaired esophageal atresia
Cystic fibrosis
Hiatal hernia
Repaired achalasia
Lung transplantation
Family history of GERD
Barrett's esophagus
Esophageal adenocarcinoma

Table 91.4 Symptoms of GER in children

Vomits with weight loss
Rumination
Irritability
Anemia – hematemesis
Feeding problems
Chest pain – abdominal pain
Dysphagia
Stricture
Aspiration pneumonia and lung abscess
Laryngospasm – hoarseness
Reactive airway disease
Chronic cough
Choking, otitis, sinusitis
Apnea
Seizure-like events
Sandifer's syndrome
Infantile arching

Regurgitation is, by far, the most common symptom of GER in infancy. A distinctive type of regurgitation begins early in infancy, usually within the 1st week of life. The regurgitation usually is effortless and occurs with burping or when the infant is returned to his or her crib after feeding. The vomitus does not contain blood or bile. This type of vomiting, termed chalasia, is benign and self-limited and rarely requires more than the simplest of treatment [210]. Occasionally, however, the regurgitation or vomiting is forceful or even projectile so that other causes, such as pyloric stenosis, must be considered. Most babies with such vomiting grow normally and do not develop other complications. Carré's study of the natural history of refluxing infants found that almost two thirds were asymptomatic by 2 years of age without treatment and that most improved before or at the time of weaning to solid foods [60]. Vomiting of this character may be considered physiologic and requires little in terms of either diagnosis or treatment.

A considerable number of vomiting infants develop significant problems. Some fail to thrive and become malnourished due to the vomiting. Others refuse feedings; perhaps swallowing is painful because of esophagitis [141]. Irritability is another symptom, which like refusal to eat, may be secondary to esophagitis and its associated discomfort. Respiratory symptoms are particularly important in babies with GER and range from coughing, wheezing, or stridor secondary to aspiration to acute life-threatening respiratory events such as apnea and near-miss sudden infant death syndrome (SIDS) [82, 159]. Because many respiratory symptoms in infants obviously arise from other sources, primarily the lungs, the causal relationship between such symptoms and GER is essential to determine prior to surgical treatment [9, 153]. Gross aspiration of gastric contents obviously can produce pneumonia, but this mechanism is rare with GER. Microaspiration with acidification of the trachea is more common, leading to laryngospasm or bronchospasm [290].

Spasm of the larynx and bronchi may also be caused by gastric acid stimulation of vagal afferents in the esophageal wall. Esophagitis probably enhances this mechanism [82, 153].

The effects of GER on premature infants with respiratory problems have been studied [138]. Most of these infants were intubated for varying periods owing to respiratory distress syndrome or bronchopulmonary dysplasia. In the former group, GER was responsible for deteriorating pulmonary status requiring reintubation. In the latter, deterioration of pulmonary status plus failure to thrive and anorexia led to the diagnosis of GER. All improved with correction of the GER [286].

In children, in contrast to infants, regurgitation is less frequently seen, and the symptoms of esophagitis predominate, as with adults. Heartburn, or substernal pain, is common.

The pain is increased with acid juices and relieved by antacids. There may be pain on swallowing. Some of the children also complain of dysphagia. The esophagitis may progress to stricture with severe obstructive symptoms in addition to pain. Carré's long-term study of untreated children found that about 4% developed strictures. With better management, that figure is now substantially lower.

Barrett's esophagus denotes a condition of metaplasia of the squamous epithelium of the lower esophagus with replacement by columnar epithelium. Chronic injury by reflux of gastric contents into the esophageal epithelium is

thought to be responsible. Although Barrett's esophagus does not produce specific symptoms, the condition is serious owing to the potential complications of stricture, ulcer, and adenocarcinoma. More than half of the children have associated strictures [124, 230]. Neither the response to treatment nor the risk of carcinoma in these children is as yet clearly defined. These children are obviously at high risk, and vigorous treatment to control or eradicate the reflux plus long-term surveillance is imperative.

The child with Sandifer's syndrome moves his or her head, neck, and sometimes upper trunk into strange and contorted positions. Torticollis without spasm of the neck muscles is common. The neck may be extended or twisted. The movements may be more striking with eating but cease with sleep. This syndrome, although rare, is associated with GER [189]. Owing to dystonia and bizarre posturing of the head, neck, and back, some children may be misdiagnosed as having a neurologic or even a psychiatric disturbance when the problem is GER and the solution is appropriate management of the reflux [46].

Diagnosis

Diagnostic procedures other than clinical evaluation should be used when the results will strongly influence treatment or will identify complications [98, 164]. For the infant with frequent regurgitation but who is thriving and is otherwise well, none are needed.

Tests are useful to document the presence of pathologic reflux or its complications to establish a causal relation between reflux and symptoms, to evaluate therapy, and to exclude other conditions. No test can address all of these questions, so test must be carefully selected and the limitations of each test must be recognized.

Radiologic Examination

When the diagnosis of obstruction is considered or when complications of GER are present, a barium study of the esophagus, stomach, and duodenum is appropriate. In expert hands, the diagnosis of reflux itself is made with a high degree of accuracy. A skilled, experienced radiologist is essential. Associated abnormalities are relatively uncommon, but conditions such as esophageal stricture, hiatal hernia, achalasia, tracheoesophageal fistula, pyloric obstruction, intestinal malrotation, or some other anatomic lesions responsible for vomiting can occasionally be clearly identified [5]. The barium study provides important anatomic information not available by other tests. However, the study is rarely useful for quantitation of the reflux. Routine performance of upper gastrointestinal series to diagnose reflux or GERD is not justified [309].

The radiologist can also evaluate the esophagus with respect to possible structural or mucosal irregularities. Esophageal peristalsis also may be usefully evaluated together with an estimation of the efficiency of esophageal clearance. Owing to the inert nature of the barium meal, the study does not permit a critical evaluation of gastric emptying.

Scintigraphy

This technique, using a technetium isotope, would appear to have a number of advantages. Reflux is accurately demonstrated. The study can be prolonged for perhaps an hour until the isotope has left the stomach, thus permitting images to be taken while the infant is quiet and undisturbed. It can be used with meals or formulas that neutralize gastric acidity, an advantage over pH monitoring in this circumstance. Some measure of esophageal clearance is possible. Evaluation of aspiration by detection of the isotope in the lungs would be a major contribution from the technique, but, unfortunately, its sensitivity for this purpose is low [21, 99]. Late postprandial acid exposure detected by pH monitoring may be missed with scintigraphy. The technique is of use in measuring gastric emptying. Nuclear scintigraphy is not recommended in the routine diagnosis and management of GERD in infants and children.

24-h Esophageal pH Monitoring

This technique was developed in the early 1970s for use in adults [150], but it was soon adapted for children [35]. A pH electrode of appropriate

size is positioned transnasally at the junction of the middle and lower thirds of the esophagus (usually 2.5–3 cm above the LES). The pH is continuously measured and recorded either on a strip chart or by a computerized pH recorder. A pH of 4.0 or less denotes reflux of acid gastric contents. The frequency and duration of reflux episodes are recorded. The number of such episodes longer than 5 min, the longest episode, and the percentage of time with pH less than 4.0 are also determined RI. An RI >7 % is considered abnormal, an RI <3 % is considered normal, and RI between 3 % and 7 % is indeterminate. RI is the most commonly used summary score. Finally, with the help of a parent or nurse, the relationship of reflux to a variety of activities is noted: sleeping, position, eating, and symptoms. Normal values have been determined, and a number of patterns of reflux have been demonstrated [66–151]. In the past, the study usually was performed in the hospital, but many are now being done quite satisfactorily at home. The test is the most reliable study available for finding occult episodes of reflux and for correlating reflux and symptoms [35]. The percentage of time the pH is under 4.0 (reflux index) is clinically useful as well as reliable with a sensitivity and specificity of 94 % or more [151].

The 24-h pH monitoring study is indicated in the following several specific circumstances:

1. Infants who have respiratory symptoms (apnea, near-miss SIDS)
2. Infants who are irritable, intractably crying, and anorectic
3. Children who have reactive airway disease (asthma) or unexplained or recurrent pneumonia
4. Children who are unresponsive to medical measures and in whom the role of GER in their symptoms is uncertain

Also, the study should be done in those children who again become symptomatic after fundoplication. On the other hand, the study generally is not useful or necessary for infants with uncomplicated regurgitation, children with esophagitis already found by endoscopy and biopsy, and children with dysphagia or heartburn thought to be caused by GER. Three patterns of reflux have been described in symptomatic infants as determined by extended esophageal pH monitoring [151]: continuous, discontinuous, and mixed. Those infants with the discontinuous type rarely required a surgical antireflux operation, whereas approximately half of those with the other two types did. One should keep in mind that medical treatment at the time of this study was much less effective than in the early 2010s. Nonetheless, this study indicates that pH monitoring can be useful in sorting out infants with GER who may or may not require an antireflux procedure [66, 148]. Incidentally, all of the infants in this study, including normal controls, refluxed frequently in the first 2 h following feeding (apple juice for this study). Esophageal pH monitoring is insensitive to weakly acid and nonacid reflux events. Abnormal esophageal pH monitoring has not been shown to correlate with symptoms severity in infants. But multiple case series report the use of esophageal pH monitoring to select the children reported to benefit from antireflux surgery.

Manometry

Esophageal manometry measures esophageal peristalsis, upper and lower sphincter pressures, and the coordinated function these structures during swallowing.

Manometry is responsible for much of our knowledge concerning GER. Maturation of the LES in early infancy was first demonstrated by this technique, only to be disputed later with the advent of more sophisticated micromanometric assemblies [214, 215]. The crucial importance of TLESR to reflux changed our entire concept of the cause of GER. The technique demonstrates normal and abnormal patterns of esophageal peristalsis and clearance. Pharyngeal swallowing has been shown to be the primary factor in clearing refluxed gastric fluid in the esophagus by a study using esophageal pH monitoring in conjunction with manometry. Development of smaller and more sophisticated pressure transducers and recording devices has permitted 24-h esophageal motility monitoring on an ambulatory basis. With

this method, deterioration of esophageal motility has been shown to parallel increasing degrees of esophagitis secondary to reflux in adults, and its use has been extended to children [284].

Esophageal manometry may be abnormal in patients with GERD, but the findings are not sufficiently sensitive or specific to confirm a diagnosis of GERD, nor to predict response to medical or surgical therapy. Manometric studies are useful to confirm a diagnosis of achalasia or other motor disorders of the esophagus that may mimic GERD. It does have a role in the child with a repaired esophageal atresia who develops reflux [269]. The lower esophagus in such a child characteristically has poor and disorganized peristalsis, and such an impairment is a major factor in determining treatment. Actually the most promising device that needs further development is the "sphinctometer" a solid-state "sleevelike system" that has been reported to record LES pressure in the ambulatory setting. The major advantage of this system is that it does not require any water infusion; therefore, it is convenient for prolonged LES pressure recording in the ambulatory setting [238]. However, only a handful of studies have been reported with this system, and it is not clear whether it can record TLESRs, the major mechanism of gastroesophageal reflux in normal subjects and patients with reflux disease.

Multiple Intraluminal Impedance

We have always assumed that retrograde flow of acid material from the stomach to the esophagus was the basic pathologic event of reflux disease. However, the situation has never been this straightforward. Trying to tie symptoms other than spitting and vomiting to pH-probe-detected reflux episodes has been particularly problematic. For example, in babies with spells of choking or colicky crying, a close association between pH-probe-detected acid reflux and these symptoms is not routinely found. Some spells coincide with episodes, but many do not.

With the use of the impedance monitor, which measures the movement of fluids, solids, and air in the esophagus rather than luminal pH changes, we are able to learn more about what is really going on in the esophagus [319].

During the last years some studies have evaluated esophageal impedance monitoring in adults and children, and these studies also raise more new questions.

The studies [312] indicate that the pH probe does not simultaneously detect the majority of reflux events defined by impedance monitoring, presumably because the fluid boluses are not acid.

Multichannel intraluminal impedance (MII) allows detection of bolus movements without the use of external radiation or radiolabeled substances. The principles of MII are based on changes in resistance to alternating electrical current (impedance) induced by the presence of various boluses within the esophagus. The timing of changes in multiple impedance-measuring segments in the esophagus allows determination of the direction of bolus movements. Combined MII and manometry provides simultaneous information on intraesophageal pressures and bolus transit, offers the ability to monitor all types of reflux, and allows the detection of the physical (liquid, gas, or mixed) and chemical (acid, non-acid) characteristics of the gastroesophageal refluxate [298].

Infants receive frequent milk feeds, and because milk is a potent buffer of gastric acidity, esophageal impedance should detect more reflux than pH recording. Indeed, impedance has the advantage over pH monitoring of being independent of pH, being better adapted to measure reflux during postprandial periods when reflux is buffered and to detect symptoms associated with non-acid or weakly acid reflux episodes. The high cost of the material and the investment in time necessary for interpretation of the recording remain a handicap in pediatrics [308].

The enhancement of the esophageal impedance may significantly change the definition of what is normal and what is abnormal for one of the most common conditions we treat [316].

Combined multichannel intraluminal impedance and pH-metry (MII-pH) is a technique that enables monitoring of gastroesophageal reflux independent of its acidity. Nonacid reflux can be associated with symptoms in patients with GERD symptoms.

The ability to detect non-acid or weakly acidic reflux events and to discern true reflux events from swallows could make it a more powerful tool than pH detection alone. Studies done in normal subjects and in GERD reveal that non-acid or weakly acidic reflux occurs frequently. MII has revealed non-acid reflux to be less common in untreated GERD subjects than in normal subjects. GERD subjects have greater degrees of liquid-type reflux events compared to normal subjects who have more gas-type reflux events. In treated GERD subjects and normal subjects, proton pump inhibitors do not seem to decrease the amount of reflux but render the non-acid or weakly acidic in nature [319, 328].

Multiple intraluminal impedance and pH electrodes can and should be combined on a single catheter and will provide useful measurements. Ambulatory MII-pH monitoring is a diagnostic tool, which is capable of detecting more than one type of reflux and achieves higher sensitivity and specificity to detect GERD than endoscopy or pH-metry. It is useful in patients with either typical or atypical reflux symptoms who are refractory to proton pump inhibitor therapy [136]. pH/MII facilitates a more focused therapeutical approach to patients with PPI-resistant GERD [17].

What is the real role of the multichannel intraluminal impedance technique in infants and children [303]?

New diagnostic trends: The acid rereflux, "acid clearing, the interval while intraesophageal pH is <4 after a traditional acid reflux event (RE)," is a potential "blind spot" during pH monitoring, when reflux of acidified gastric contents may occur undetected by the pH probe. This is termed "acid rereflux" [266]. Detecting acid rereflux in addition to traditional acid rereflux is most likely to occur in patients with severe esophagitis, postprandially, and in the recumbent acid provides a more reliable indication of the severity of antireflux barrier incompetence than the pH probe alone [242].

The combination of MII with manometry enables determination of the relationship between esophageal pressures and flow and, therefore, enhances evaluation of esophageal function in terms of assessment of mechanisms of esophageal volume clearance. This technique will improve our understanding of physiological mechanisms in pediatric GERD.

To distinguish primary peristalsis (to bolus swallowing) from secondary peristalsis (to spontaneous esophageal clearance) and to calculate the time of spontaneous bolus clearance (BCT) based on 24-h monitoring and multichannel intraluminal impedance allowed to determine the impact of surgical treatment [81]. So new diagnostic tools such as combined MII and pH-metry and Bravo capsule are described by some authors. Innovative techniques such magnification, narrow band imaging, and computed virtual chromoendoscopy are also reviewed [317].

Ultrasonography

Ultrasonography is not recommended as a test for GERD but can provide information not available through other technology. It can detect fluid movements over short periods of time and non-acid efflux events, can detect hiatal hernia, length and position of the LES relative to the diaphragm, and magnitude of the gastroesophageal angle of His. At present, there is no role for ultrasound as a routine diagnostic tool for GERD in children because there are low specificity (11 % color Doppler 15 min postprandially) but 95 % sensitivity when compared with the results of 24-h esophageal pH testing [149].

Endoscopy and Biopsy

Suspicion of esophagitis is the prime indication for this diagnostic technique. Irritability and anorexia in infants and heartburn or upper abdominal pain in children raise this suspicion. Dysphagia is another indication. The study is of particular value in NI children with vomiting, growth failure, and other confusing symptoms. The endoscopist may be unable to discern esophagitis on gross inspection [24, 197]. One study recorded abnormal mucosa in only 52 % of children with documented reflux. When the study showed inflammation, however, the finding was 100 % specific, and mucosal inflammation was found in none of the nonrefluxing patients. Owing to the lack of sensitivity of esophagos-

copy alone, mucosal biopsies are essential. Biopsies and microscopic diagnoses are both highly specific and sensitive (95 %) in the diagnosis of esophagitis [25, 68]. The histologic criteria for esophagitis on biopsy examination are well established. Intraepithelial inflammatory cells, eosinophils particularly, and morphometric measures of basal cell layer thickness and papillary height are highly specific for esophagitis. Clearly, the biopsy diagnosis of esophagitis is a most important finding because it demands prompt and vigorous treatment. The primary role for esophageal histology is to rule out other conditions in the differential diagnosis; GERD is likely the most common cause of esophagitis in children, but other disorders such as eosinophilic esophagitis, Crohn's disease, infections (*Candida albicans*, herpes simplex, cytomegalovirus), caustic ingestion, and connective tissue disease, graft-versus-host disease postsclerotherapy, radiation, and chemotherapy also cause esophagitis.

Esophagoscopy shows other esophageal abnormalities as well, particularly ulcer, stricture, and Barrett's esophagus. All three are severe complications of long-standing reflux and often coexist. Combining 35 patients from three separate studies on Barrett's esophagus in children, 16 strictures were identified [68–117]. The endoscopist often does not recognize the characteristic pink-red velvety appearance of Barrett's esophagus, emphasizing the importance of biopsies. The typical gross appearance of Barrett's esophagus at endoscopy occurs in only a minority of patients; the diagnosis rests on histologic biopsy examinations [68, 75]. Three types of metaplastic columnar epithelium may be identified: cardiac, fundic, and intestinal. There does appear to be some correlation between the type of columnar epithelium found and the potential for dysplasia or carcinoma [122].

In addition to esophagitis and its complications, esophagoscopy also may show isolated patches of gastric epithelium, thought to be of congenital origin, in the proximal esophagus. Postoperative complications of repaired esophageal atresia, such as stricture or recurrent fistula, may be visualized.

Summary of Diagnosis and Clinical Findings

Consideration of the symptoms, on the one hand, and the results of investigation on the other enable the diagnosis of GER to be made with a high degree of certainty. Abnormal physical signs may not exist, but note should be taken of the child's habitus and pulmonary findings. Despite knowledge of the natural history of GER, diagnostic delay is by no means unusual, particularly in those children whose GER leads to failure to thrive or in the group with respiratory problems. In these two groups in particular, various differential diagnoses must be considered, always bearing in mind that GER frequently coexists with other conditions. This is particularly true when GER is associated with comorbidity, as in children with neurological impairment or following esophageal atresia repair.

The following diagnoses can be recognized, but there may be overlap from one group to another.

1. The "spitters": These represent the majority of babies and infants with GER and have been well described by Jolley. A clinical diagnosis can usually be made, but under special circumstances, including parental anxiety, limited investigation may be required – rarely more than a radiographic study. Provided adequate explanation is combined with appropriate communication, there is no reason why this need adds to parental anxiety.
2. Where clinical suspicion is high, but the diagnosis may be in doubt. In this group, further investigation is required and this may take the form of 24-h pH-metry, multiple intraluminal impedance or esophagoscopy and biopsy or both.
3. Additional symptoms are present, e.g., irritability and "heart burn" (which is difficult to evaluate in children), and thorough investigation is essential, the nature of which will depend on modalities available. Manometry may be helpful; gastric scintigraphy has a definite role. In the final analysis, the pathway to follow is ideally the same as for the second group.

4. Clinical suspicion is aroused and investigation reveals an esophageal stricture. Endoscopic examination will usually determine the severity and response to dilatation.
5. When Barrett's esophagus is present, the symptoms are those of GER and/or an associated stricture.
6. Respiratory symptoms dominate the clinical picture – either the GER produces these symptoms or GER is a result of respiratory tract disease. This group requires a high degree of suspicion, particularity with asthmatic children or following repair of esophageal atresia, which should lead to appropriate investigation [256].
7. A miscellaneous group, including the Sandifer's syndrome, and in the neurologically impaired child [167, 280].

ln summary, therefore, diagnosis of GER should not be difficult, but difficulties arise, particularly when the symptomatology is atypical. Particular note should be taken of respiratory features because life-threatening episodes may be associated with aspiration into the respiratory tract.

It is important to know the technical aspects, indications, advantages, and disadvantages of each diagnosis method in order to appropriately use any of these tests.

History

Bright, in 1836, called attention to a partial stomach herniation, although there had been previous references in the literature (Billard P 1828 and Frank JP 1950).

During the following century, various authors described esophageal lesions, peptic esophagitis, hiatal hernia, and esophageal stenosis without relating their pathogenesis until 1935, when Winkelstein described for the first time the gastroesophageal reflux syndrome, already suggested by Jackson in 1922. Allison, in 1943 and 1951, described the pathogenesis and physiopathology of gastroesophageal reflux and suggested an anatomical repair of the hiatal hernia. In 1947, Neuhauser and Berenberg [210] brought reflux to the attention of pediatricians and coined the term "echalasia"; they outlined the clinical findings and suggested positional therapy for reflux.

Carré [59, 60] who described the "thoracic stomach" and demonstrated the salutary therapeutic effects of gravity on infants in the upright position and Roviralta [258, 259] who developed the concept of phrenicopyloric syndrome, in the 1950s, offered a basis for conservative treatment. Since the late 1960s, GER has increasingly been recognized as a condition that affects children frequently and, at times, with serious consequences. In the 1960s, it was characterized by the appearance of various types of operative procedures. Lortat-Jacob, Hill, Belsey, and Nissen and Rosetti [211] contributed most importantly to the operations employed today. From the 1960s to the present, the greatest progress has been made in diagnostic methods and in the investigation of the pathogenesis of gastroesophageal reflux and its complications. In 1977, Casasa and Boix-Ochoa assessed MAO as an objective indication of the need for operation. Normal secretion after stimulation with pentagastrin in an infant, according to the method described, is below 5 mEq/h/10 kg body weight. In symptomatic patients, gastric secretion did not recede, and MAO levels higher than 5 mEq/h/10 kg were observed. In 250 patients studied with this test, failed postural treatment was usually accompanied by a high MAO. In the last years, esophageal manometry, esophagoscopy and esophageal biopsy, "esophageal clearance" and immunologic defense of the esophageal mucosa, acidity tests, 24-h pH esophageal monitoring, scintiscan, alterations in gastroduodenal motility, duodenogastric reflux, multichannel intraluminal impedance, and factors that influence the peptic activity of the gastric content on the esophageal mucosa have been the subjects of publications.

Gastroesophageal reflux is perhaps one of the aspects of pediatric surgery that has advanced most over the last few years and generated the most interest, due to its variety of pathologic manifestations and associated complications. Synonymous for a long time with "hiatal hernia," that term has been abandoned for the more appro-

priate "gastroesophageal reflux," which denotes the incompetence of the antireflux barrier, while "hiatal hernia" only describes an anatomical anomaly that may or may not be accompanied by reflux.

Until the 1990s, medical treatment was relatively ineffective, and in all likelihood most of those babies and children who did become asymptomatic were taking advantage of the natural course of the disease. This left a large number who continued to have significant, at times life-threatening, complications, and surgeons eagerly rushed to fill this void. A number of effective and safe antireflux procedures were developed during these years, and by adopting one or more of these techniques, pediatric surgeons were soon performing large numbers of such operations [31–211]. Antireflux procedures now rank second or third in frequency of major operations performed by pediatric surgeons. Long-term results in several large series are excellent with open surgery, and complications are relatively few [108]. However, significant complications and failures do occur, and long-term results, although generally good, are by no means perfect.

At least two major advances in management are changing the therapeutic scenario in GER. First, of most importance, the proton pump inhibitor omeprazole has revolutionized medical treatment. This drug cures esophagitis with an effectiveness that is truly amazing in comparison with antacids, histamine receptor antagonists, and motility-enhancing drugs. Second, antireflux operations are being performed laparoscopically in increasing numbers. Although not a fundamental change in concept, this technique has proved to reduce both short-term postoperative morbidity and long-term complications such as intestinal obstruction.

In addition to these clinical advances, basic investigations have focused on mechanisms of reflux and emphasized the cause of reflux itself and the patterns and effectiveness of esophageal clearance. Much information has come from studies of lower esophageal pressure profiles in normal human beings and in patients with reflux esophagitis [88]. A wide variation in the basal LES pressures was found that bore little relationship to reflux, refuting the widely held concept of a direct relationship between a low basal LES and reflux. Instead, reflux occurred most often during periods of inappropriate, complete LES relaxation. These relaxations were inappropriate in the sense that they were not secondary to esophageal peristalsis initiated by pharyngeal swallowing.

These findings have been confirmed, and the proposition that such inappropriate LES relaxations are the primary mechanism leading to reflux has been widely adopted. Additional research using similar technical approaches has expanded our knowledge of esophageal peristalsis, normal and abnormal, the role of the diaphragm in prevention of reflux, and the unsolved question of delayed gastric emptying (DGE) as important factors in this knotty puzzle. Our understanding of the multiple and complex factors controlling the esophagogastric junction has increased remarkably but remains far from complete.

The detection of gastroesophageal reflux has been limited to acid exposure observed on 24-h pH monitoring. It is clear that non-acid reflux can be a significant clinical problem. Impedance technology with the capacity to detect all types of reflux (acid, non-acid, liquid, mixed, and air) has allowed to redefine GER. Over half of GER events were not detected by pH studies [15].

GERD has multiple etiologies, and understanding of these is important for determining which patients are the best surgical candidates. Proton pump inhibitors have become the mainstay of current treatment for primary GERD. Although laparoscopic surgery appears to be better than open surgery, there remain some morbidity and complications that careful patient selection can minimize. So, surgery for GERD should be performed only after failure of medical management or for specific problems [187].

Medical Treatment Approaches

After GER has been detected and diagnosed, the question is, which treatment should be applied, conservative or surgical? [31]. The decision

should be individual, depending on age, anatomical type, severity, and social environment. In the majority of cases, conservative treatment is the therapeutic of choice.

Conservative treatment is based on three pillars, feeding, posture, and drugs, which combined have the effect of potentiating the natural tendency of GER towards cure [72–223]. With this treatment, we have obtained 90 % of good results in 3,000 patients of less than 1 year, with a follow-up of more than 25 years in some cases and with the experience that each single patient needs his own tailored treatment.

Dietary Modifications

The emptier the stomach, the less possibility of vomiting; therefore the rule was less volume, more frequently, so it is almost important to avoid the preservation of large gastric volumes available to reflux.

It is difficult to formulate dietary guidelines for children with GERD. However, it should be taken into account that whatever diet is formulated, the nutritional needs of the infant should always be satisfied. In older children, dietary suggestions include a diet with normal to low fat and the avoidance of chocolate, coffee, tea, gaseous drinks, and spicy foods.

If emesis persists despite postural therapy and dietary recommendations including milk thickening, acid alginic can be given. The latter works by forming a floating viscous layer on top of the gastric contents and has been shown to decrease emesis frequency as well as intraesophageal acid exposure in infants and older children with symptomatic GER [53].

Thickening of infant formulas can be useful to reduce the frequency of emesis. It is possible that the increased viscosity of thickened feedings determines a more prolonged persistence a food in the stomach; however, controlled studies by using intraesophageal pH testing have shown that thickened feedings do not always reduce esophageal acid exposure as measured by intraluminal pH-metry [14]. It is likely that uncontrolled thickening of feeds can give rise to high-osmolality or high-viscosity meals with consequent gastric emptying delay and triggering an increase of reflux episodes as a result of TLESR [263].

In older children and adolescents, lifestyle changes include modification of diet and sleeping position, weight reduction, and smoking cessation.

Positional Therapy

The seated semi-upright position for an infant with reflux has been recommended since 1956 [60]. In the 1960s Carré showed that 60 % of children with GER treated in this way improved by the age of weaning and an additional 30 % improved by 4 years of age [59]. Other studies confirmed the effectiveness of this approach [259], and in Europe positional therapy in the chalasia chair remained the therapy of choice for many years. However, it is possible the improvement found in the symptoms was simply due to the natural evolution of the illness since a series of articles published between 1976 and 1983 showed by means of pH monitoring the semi-upright position worsened GER both in adults [84] and children [224, 243]. The European Society of Gastroenterology and Nutrition (ESPGAN) then recommended to lie babies in semi-elevated prone position until, in 1993, the British Department of Health recommended lying babies in the supine position, as prone position was found to be an independent risk factor for sudden infant death syndrome. Today, the ESPGAN still recommends the 30° prone position, but only as the second step after thickening of feedings has failed in improving symptoms.

In our experience, a program of semi-seated position (30–45°) 24 h a day and thickened and frequent small feedings to avoid overfilling the stomach gives satisfactory results in 80–90 % of babies under 14 months of age. Once instituted, this regimen should be continued for at least 6 months.

Failure of postural therapy may be related to social problems, chronic infections, or impaired

gastric clearance. In older patients postural treatment is impractical because of the virtual impossibility of maintaining the desired semi-sitting posture. Close attention to the details of how this plan is followed by the family members is most important to its success [223].

Esophageal pH and combined pH/MII monitoring show that reflux is quantitatively similar in the left-side-down and prone positions. Adolescents, like adults, may benefit from the left lateral decubitus sleeping position with elevation of the head of the bed.

Pharmacological Therapy

If symptoms persist despite a well-monitored program of postural therapy and dietary modifications, pharmacologic measures should be added.

Medical therapy includes the administration of one or more drugs that either increase esophageal peristalsis, increase LES pressure, increase gastric emptying, or lessen gastric acid production. In the last years the pharmacological therapy has changed.

The Prokinetic Drugs

The prokinetic drugs (bethanechol, metoclopramide, domperidone, cisapride) that were ordinarily tried first now are a second option. The drug most commonly used in the past which was cisapride (0.2–0.3 mg/kg dose) nowadays has been demonstrated that produces prolongation of the Qtc interval on electrocardiogram, and its use has been restricted to limited access, finding increasing risk of sudden death syndrome [239].

Although it has not been proven to diminish the frequency of TLESR, it increases the basal pressure of the sphincter, improves esophageal clearance, and accelerates gastric emptying; all are beneficial effects in the treatment pathological reflux. So, its use was been recommended by some on the basis of a clinical diagnosis alone [307] because we thought that cisapride was free from significant side effects. The experience has demonstrated the opposite. Because of recent concerns about safety, a critical and in-depth analysis of all reported adverse events was performed and resulted in the conclusions and recommendations by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition that cisapride should only be administered to patients in whom the use of prokinetics is justified according to current medical knowledge. If cisapride is given to pediatric patients who can be considered healthy except for their gastrointestinal motility disorder, and the maximum dose does not exceed 0.8 mg/kg per day in three to four administrations of 0.2 mg/kg (not exceeding 40 mg/day), no special safety procedures regarding potential cardiac adverse events are recommended. However, if cisapride is prescribed for patients who are known to be or are suspected of being at increased risk for drug-associated increases in QT interval, certain precautions are advisable [18]. Such patients include those (1) with a previous history of cardiac dysrhythmias, (2) receiving drugs known to inhibit the metabolism of cisapride and/or adversely affect ventricular repolarization, (3) with immaturity and/or disease causing reduced cytochrome P450 3A4 activity, or (4) with electrolyte disturbances. In such patients, ECG monitoring to quantitate the QT interval should be used before initiation of therapy and after 3 days of treatment to ascertain whether a cisapride-induced cardiac adverse effect is present [179].

Measures to reduce gastric acidity should be added to this regimen in patients with complicated reflux, especially with esophagitis [91].

Histamine

H2 receptor antagonists decrease acid secretion by inhibiting histamine 2 receptors on gastric parietal cells. In one study of infants, ranitidine (2 mg/kg per dose orally) reduces the time that gastric pH is <4 by 44 % when given twice daily and by 90 % when given three times per day [287].

H2 receptor antagonists have a beneficial effect for patients whose respiratory symptoms are suspected of being caused by microaspirations. Other H2 receptor antagonists, such as cimetidine, have been associated with an increased risk of liver disease [247] and with gynecomastia [112].

Proton Pump Inhibitors

An antisecretory agent, omeprazole, has been demonstrated to reduce gastric acid production to zero [142–332]. It is a very powerful drug that affects gastric acid production for 72 h after cessation of administration. Proton pump inhibitors inhibit acid secretion by blocking Na+/K+ ATPase, the final common pathway of parietal cell acid secretion, often called the proton pump.

A prospective study determined the therapeutic dose range (0.7–3.3 mg/kg/day), efficacy, and safety of omeprazole for children. Up to date, changes due to hypergastrinemia observed in the gastric mucosa of children with long-term treatment with the drug (up to 4 years) are benign (fundic polyps, expansion of the parietal cells, and pseudohypertrophy of individual parietal cells) [127, 147].

Actually proton pump inhibitors (PPIs) are mainstay of treatment of the GER disease in children, because all the antacids or histamine receptor agonists (H2RAs) reduce acid secretion only by competing with the histamine receptor located in the parietal cell membrane, but the parietal cell receptors that responds to endocrine or vagal stimulation are not affected and there is not an effective blockade of the gastric acid production.

The pharmacology of every PPI involves targeting the gastric acid or proton pump (H+/K+-ATPase), which is situated in parietal cell membranes. Active drug irreversibly binds to cysteine residues within the H+/K+-ATPase via a covalent bond. Consequently, PPIs inhibit the final step of gastric acid secretion by blocking proton production [235].

Experience with these drugs in children indicates that they can be used in very resistant esophagitis and in special situations, such as GERD in neurologically impaired individuals. An initial dosage of 0.7 mg/kg/day has been suggested, with subsequent adjustment by repeated prolonged intraluminal esophagogastric pH-metry [142, 332].

A study has shown that omeprazole is highly effective even in grade IV esophagitis [143]. A dosage of 0.7 mg/kg/day healed 45 % of patients and 1.4 mg/kg/day healed another 30 %. On a body weight basis, the dosages required in children are generally higher than those in adults. For children unable to swallow the whole capsule, it is suggested to open the capsule and give the granular contents in a weakly acidic vehicle such as orange juice, yogurt, or cranberry juice. The granules are stable in acid but are degraded in a neutral or alkaline pH. Actually new PPIs competing in excellence are in the market: lansoprazole, rabeprazole, pantoprazole, esomeprazole, and dexlansoprazole in the line to offer better medical possibilities [1, 62, 171, 265].

But the pediatric surgeon has to bring to discussion if we are delaying the final treatment, looking for a better quality of life. PPIs appear to be well tolerated for short-term use (3–7 months), but studies to assess long-term safety are needed because the significance of chronically elevated gastrin levels in children is unknown.

There are potential risks associated with acid suppression results from PPI therapy in infants [226].

There are four main categories of adverse effects related to proton pump inhibitors: idiosyncratic reactions, drug-drug interactions, drug-induced hypergastrinemia, and drug-induced hypochlorhydria. Idiosyncratic side effects occur in up to 14 % of children taking this drugs. The most common are headache, diarrhea, constipation, and nauseas, occurring in 2–7 %. Every solution opens new questions. What is the effect of proton pump inhibitors PPI on gastric emptying? The delaying effect of PPI on gastric emptying of solid meals is consistent, whereas the effect of PPI on the emptying of liquids is inconsistent. Some hypothesis are that gastric emptying involves a process of peptic hydrolysis. PPIs impair the hydrolytic digestion by inhibiting acid-dependent peptic activity, thereby delaying the solid emptying. Gastric emptying of liquids largely depends on volume and energy density of intragastric contents. Hypergastrinemia has been considered to delay gastric emptying. The delayed emptying of solids due to PPI therapy may have clinical implications in the management of gastroesophageal reflux disease [264].

The GABAβ Agonist Baclofen

The GABAβ agonist baclofen recently has been demonstrated that in normal subjects, *it significantly inhibits gastroesophageal reflux* by inhibition of transient LES relaxations [180]; these findings suggest that GABAβ agonists may be useful as therapeutic agents for the management or reflux in patients with GER disease inhibiting the triggering of TLESR by acting centrally on the pattern generator in the brainstem [26–48]. Baclofen reduces postprandial acid and non-acid reflux and their associated symptoms. GABAβ agonists may have a role in treating GERD. Actually it is the most promising drug and in the next years a research field as the major inhibitory neurotransmitter within the central nervous system controlling the rate of TLESRs, the key mechanism underlying most episodes of GER. Compared with other available agents, baclofen is available as an oral agent and does not have adverse effects on basal LES pressure or acid clearance. Side effects are common, however, and include drowsiness, nausea, and the lowering of the threshold for seizures. It is hoped that new compounds with more specific and better targeted action will be developed in the future [109, 248, 312] (Table 91.5).

Surgical Treatment Approaches

Surgery is the next step and one that should be effected without delay when conservative treatment fails or age, type of anatomical anomaly, severity, respiratory complications, and social environment make it necessary. In the 1990s effective and safe antireflux surgical procedures were developed, and pediatric surgeons had been performing large numbers of antireflux procedures. In the 2000s they continue to rank second or third in frequency of major operations performed by pediatric surgeons. At present, a surgical decision is easier to make than 25 or 30 years ago, seeing as short- and long-term results and few complications make this a safe therapeutic method with very few risks [106]. On the other hand, results of surveys affected among parents show that 97 % of them were satisfied with the postoperative results, different from surgery in adults, whose symptoms persist in 27–54 % of patients. All the surgical techniques are good, but have a different philosophy.

A variety of operative techniques result in long-term control of reflux with low mortality and few complications [36–158, 278, 315].

Table 91.5 Therapy of reflux

Conservative
Position – semi-seated
Avoid large meals, tight clothing
Avoid foods and medications that lower LES
Pharmacology
Proton pump inhibitors
TLESR inhibitors: GABA – baclofen
Surgical: laparoscopic fundoplication
Two philosophies:
Restoring physiology
Boix-Ochoa, Thal, Toupet
Creating a valve: Nissen fundoplication

Nissen Fundoplication

Two different concepts govern the most commonly used operative procedures. In the first, a "tight valve" is constructed as a permanent substitute for the child's ineffective antireflux mechanism. The Nissen FP is the prototype utilizing this concept. Recent research in adults suggests that this "mechanical mechanism" has its functional counterpart in the form of inhibition of triggering of transient LES relaxations and prevention of the completeness of LES relaxation.

In the second concept, the aim is to correct the abnormal anatomy so as to permit the normal physiological antireflux mechanisms to become effective.

Thal-Ashcraft and Boix-Ochoa Techniques

The Thal-Ashcraft and the Boix-Ochoa operations are examples. The essentials of these approaches are provision of a sufficiently long intra-abdominal esophagus, fixation of the

intra-abdominal esophagus in place, and restoration of the angle of His. Both the Thal-Ashcraft and the Boix-Ochoa techniques allow a physiologic degree of GER, avoid gas bloat, and even permit vomiting (Table 91.5).

Results of both approaches are excellent, at least in neurologically normal (NN) children, although the Nissen procedure is followed by a higher incidence of complications [126–289].

The aim of the Boix-Ochoa procedure is to restore the anatomic relationships and the physiologic characteristics of the lower esophageal sphincter mechanism (Fig. 91.2). This may be achieved by restoring the length of the intra-abdominal segment of the esophagus, repairing the widened esophageal hiatus in the diaphragm and anchoring the esophagus to its margins, and restoring the angle of His. The final step comprises the opening up or unfolding of the fundus of the stomach (as in opening umbrella) by inserting suspending sutures between the fundus and the diaphragm. The procedure has the effect of increasing the length of the intra-abdominal segment of esophagus, which restores the normal closing pressure mechanism. Reconstruction of the angle of His provides the mechanism for compressing and closing off the esophagus, while unfolding the fundus of the stomach buffers the effect of raised intragastric rpessure and enhances the mechanical closing of the esophagus. Between 1966 and 1992, a total of 2,566 patients were assessed for gastroesophageal reflux: 65 had major hiatal hernias. The total number undergoing antireflux surgery was 224 (8.7 %). Follow-up studies on 180 patients 2–18 years after the operation revealed excellent radiological and clinical results in 168 (93 %) cases. In 12 patients reflux could be demonstrated on radiological assessment but the children were asymptomatic. Two patients required reoperation. In this series the complications were adhesion obstruction 3, postoperative pneumonia 5, mediastinitis secondary to perforation 1, and esophageal stenosis 2 [33].

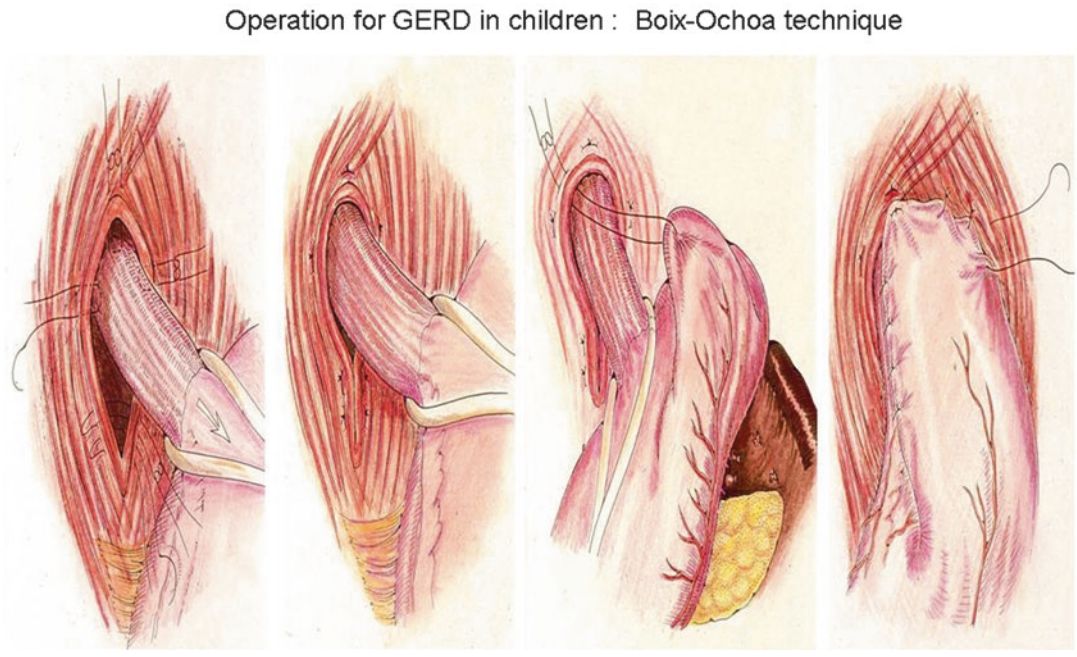


Fig. 91.2 Operation for GERD in children Boix-Ochoa. The length of intra-abdominal esophagus is restored, the esophagophrenic ligament sutured to the edges of the crura, and the crura tightened. The angle of His is restored by a suture taken from the fundus, well down on the fundus at the level of the highest short gastric vessels, to the rim of the hiatus superiorly and on the *right*. Reinforcing sutures maintaining the stomach in this position are placed between the fundus and the anterior esophageal wall. Suspending sutures tacking the fundus to the diaphragm unfold or open up the fundus like an umbrella

Still, the most widely used procedure is that described by Nissen and Rosetti [33]. The technique consists in wrapping the gastric fundus around the intra-abdominal esophagus and the gastroesophageal junction. This wrap acts as a valve to impede reflux. The Nissen fundoplication has been used much more frequently than any other operation. The lower esophagus is mobilized so that an adequate intra-abdominal length is assured. By passing the fundus from left to right behind the esophagus, a 360-degree wrap is performed. This usually requires division of at least some of the short gastric vessels. The right and left margins of the wrap are sutured together anteriorly; these sutures include the anterior esophageal wall. The superior margin of the wrap is fixed to the hiatus with a few additional sutures. The wrap should be relatively short (depending on the age of the child) and constructed loosely (floppy). The wrap transmits intragastric pressure to the lower esophagus, raises the LES pressure, and acts as an effective one-way valve. A gastrostomy is often added for a vent in case the child develops gas bloat or for feedings [52, 108]. It is almost routinely added in NI children [213].

Early postoperative complications are uncommon [177, 282]. Small bowel obstruction has been reported in 4–9 % in the first 2 years after operation [155–299]. Most of these resulted from intra-abdominal adhesions. A more significant problem is failure of the wrap, occurring in from 4 % to 12 % in the larger series [79–244]. These failures usually resulted from disruption of the wrap or herniation of the wrap upward through the hiatus. Reoperation on those with a failed wrap was successful on a long-term basis in about 75–80 %, and overall long-term good results are reported at about 90 % [177, 299, 324].

In the Thal procedure, the lower esophagus is freed and the crura approximated posterior to the esophagus as in the previous techniques. A partial, 180-degree anterior fundal wrap is then constructed; this partial wrap attaches to the intra-abdominal esophagus. Like our procedure, it is technically simpler than a Nissen procedure and has a shorter operating time. The incidence of postoperative intestinal obstruction is low (<1 %), probably due to a transverse upper abdominal incision with minimal exposure of the intestine [291]. In a series of 1,150 patients, disruption of the fundoplication and recurrent GER have occurred in only 2 % and with recurrent hiatal hernia in another 2 %. A distinct advantage of a lesser wrap is the very low incidence of gas bloat syndrome, so that a gastrostomy is rarely done. These children are able to burp or even, when necessary, vomit. Overall good results exceed 90 %. In both series, the number of NI children was low, whereas in most other large series, the incidence of NI children is often 50 % or higher [12].

Partial Wrap Method, Toupet Procedure

Another partial wrap method is the Toupet procedure, also developed to minimize the gas bloat problem. In this operation a partial, 270-degree wrap is positioned posterior to the esophagus. The preliminary steps of the technique are identical to the previous two procedures. The Toupet procedure can be performed through an upper abdominal transverse incision, so that exposure of the intestine is largely avoided. After the crura have been approximated to restore the size of the hiatus to normal, the gastric fundus is passed posterior to the esophagus. The posterior aspect of the wrap is sutured to the right crura. The margins of the wrap on either side are then sutured to the right and left margins of the esophagus, leaving the anterior esophageal wall free. Experience with this operation in 112 patients revealed that 30 % were NI [19]. The early postoperative courses were generally benign, but two developed intestinal obstruction. On late follow-up evaluation, the outcome was excellent in 90 %.

Minimal Invasive Surgery: Laparoscopic Fundoplication

Laparoscopic approaches to fundoplication are being reported with increasing frequency. In 1991, the feasibility of performing Nissen fundoplication in 12 adults using a laparoscopic

approach was demonstrated [77]. Laparoscopy has changed the promise in terms of reducing short-term postoperative morbidity and decreasing number of complications as intestinal obstruction for a reality nowadays. Pediatric laparoscopic fundoplication is achieved with five trocars placed in the upper abdomen [116].

The dissection of the histus is begun by dividing the gastrohepatic ligament, then the phrenoesophageal ligament is incised, the short gastric vessels are divided, the fundus is separated from diaphragm, and the cura is dissected. Care is taken to avoid vagal nerve trunks. For a Nissen fundoplication a 2 cm wrap is constructed with interrupted sutures by attaching the fundus to itself anteriorly at the 10 o'clock esophageal position. The fundoplication is then secured to the undersurface of the diaphragm with two or three nonabsorbable sutures to prevent migration of the wrap into the chest. A "loose" Nissen wrap is preferred. A Maloney dilator is placed within the esophagus to fully dilate it and prevent narrowing while the wrap is constructed [114]. The experience with 268 laparoscopic fundoplications showed recurrence rate about 8 %, with 12 % in the Toupet group and 5.5 % in the Nissen fundoplication group [231, 260].

In rapid succession, additional reports appeared confirming the practicability and safety of this technique in adults. To show how the pendulum has swung in some quarters vis-à-vis medical treatment, a recent report proposed laparoscopic fundoplication as a reasonable alternative to omeprazole [10]. Reports of endoscopic antireflux operations performed on children appeared soon after with documentation of both feasibility and satisfactory short-term results [115, 186]. One group's experience not only detailed the learning curve but also described a rapid drop in the percentage of cases in which conversion to an open operation was required, from 30 % after the first 20 cases to a cumulative rate of 7.5 % after 160 cases [195]. A similar drop in complication rate was also noted, falling from an early 12 % rate to a final cumulative rate of 7.4 %.

Esposito C. et al. published in 2000 results about laparoscopic approach in 289 children affected by GERD, ages between 4 months and 17 years, 141 Nissen Rossetti and 141 Toupet, and the duration of surgery was between 40 and 180 min and conversion to open surgery 1.3 %.

The same results published by Ostlie DJ et al. and length of stay 1.2 days, operating time 91 min, time to initial 7.3 h, and time to full feedings 21.8 h in laparoscopic fundoplication in children (Table 91.6) concerning length of stay.

Similar results were published by J Gill et al. also in 2007 after the learning curve of a single surgeon over a 10-year period: operative time 86 min, length of stay 1.2 days, and conversion to open operation 2 %.

The utilization of esophageal mobilization to create a 2–3 cm length of intra-abdominal esophagus has been practiced very frequently for many surgeons. Recently, a retrospective study coordinated by the Children's Mercy Hospital in Kansas City and University of Alabama in Birmingham (St Peter et al. 2010). suggested that minimal esophageal mobilization with no violation of the phrenoesophageal membrane may reduce the risk

Table 91.6 Operative conversions to open procedures decrease with experience, not the number of reoperations Gill J, Booth MI, Stratford J, Dehn TC. The extended learning curve for laparoscopic fundoplication: a cohort analysis of 400 consecutive cases. *J Gastrointest Surg*. 2007;11(4):487-92.

Percentage of conversions to open operation according to a number of patients	
1–50	16 %
51–100	18 %
101–150	12 %
151–200	10 %
201–250	4 %
251–300	0 %
301–350	0 %
351–400	0 %
Percentage of patients needing reoperation	
1–50	14 %
51–100	8 %
101–150	2 %
151–200	4 %
201–250	4 %
251–300	4 %
301–350	6 %
351–400	6 %

of postoperative migration of the fundoplication wrap into the lower mediastinum and the need for a redo operation.. This study analyzes 177 patients between 2 years, and transmigration rate was 30–7.8 %. The reoperation rate was 18.4 % in the mobilization group and only 3.3 % in the group with minimal esophageal mobilization. The mean operative time was 82.5 ± 2.2 min and 83.9 ± 21.0 min in both groups, maximal and minimal esophageal mobilization,

Transhiatal wrap migration is the dominant mode of failure after laparoscopic Nissen fundoplication with relatively high rates of reoperation reported in large case series.

As has been found in most other studies of fundoplication operations, the complications occurred significantly more often in the NI than in the neurologically normal. The early complications after laparoscopic Nissen were 41 % in NI patients versus 17 % in NN patients. The late complications occurred in 13 % of NI patients and 0 % of NN patients. The authors conclude that the laparoscopic technique is superior to the open method in the performance of Nissen antireflux procedures [144, 161].

Results

The results of the combined experience with antireflux operations from seven large pediatric surgical departments are encouraging [107] A total of 7,467 children were included. Significant clinical improvement was recorded in 94 % of NN children and in 84.6 % of the NI group. Major postoperative complications were recorded in an average of 4.2 % of the NN patients and in 12.8 % of the NI patients. These data show the significant differences between NN and NI children, but more important, they emphasize the satisfactory overall outcome in both groups.

Laparoscopic Nissen fundoplication has largely replaced open Nissen fundoplication as the preferred antireflux surgery for adults and children, due to its decreased morbidity, shorter hospital stays, and fewer postoperative problems. In a series of 456 children undergoing surgery younger than 5 years of age, Diaz et al. reported that those with laparoscopic Nissen fundoplication had a higher reoperation rate than those with open Nissen fundoplication. Average time to reoperation with laparoscopy was 11 months versus 17 months for open surgery. In children with comorbidity, the probability of reoperation was 18–24 % after laparoscopy, compared with 6–16 % for open surgery [90]. The annual number of antireflux operations has been on the increase in the United States, especially in children younger than 2 years [176]. In contrast, in adults, rates of fundoplication are declining in the United States and have dropped 30 %.

The larger question is not which operation, but, rather, when. Until the mid-1990s, the indications for surgery were reasonably easy to define. The results of nonoperative therapy for the severe or potentially dangerous complications of reflux were generally unsatisfactory; hence failure of medical management was common in those children at the highest risk of significant morbidity or even death. As a consequence of omeprazole, the most appropriate therapy for children with severe GER is evolving, and our present concepts of the indications for surgery are changing, in front of the appearance of new drugs that they have enhanced the medical treatment. But how long is the medical treatment? Which are the consequences of a long medical treatment from infancy to adulthood? That is the unsolved question!

Both medical and surgical treatments have advantages and drawbacks. Omeprazole does not control reflux directly; rather, omeprazole is effective by reducing gastric acidity almost to the vanishing point. This permits healing of even severe esophagitis in many children and prevents acid reflux into the esophagus, thus quite possibly preventing some of the respiratory complications. However, its effectiveness disappears when the drug is stopped; gastric acidity returns and the original problems of the disease reemerge. Hence, lifelong treatment appears to be a requirement for lifelong effectiveness. Fundoplication, ideally, is a one-time episode that is both effective and long lasting. Often this is true, and a number of series with long-term follow-up evaluation show highly satisfactory

eventual results in more than 90 % of the children [107] concerning long-term effectiveness and complications. Combined study with follow-up with omeprazole in children by contradict some of the data and conclusions [128]. They point to the relatively high morbidity of antireflux procedures in high-risk children such as those who are NI and those who had previous repairs of esophageal atresia. The excellent short-term results with omeprazole in these high-risk groups make the medication a viable alternative. Fundoplication is believed to be best reserved for those with proven or probable risk of aspiration from below and for the NN children whose results from surgery generally are excellent [292]. At the least, such drug therapy may provide a considerable amount of relief and permit postponement of the decision for or against surgery for considerable time.

There is no consensus on the indications for surgery in GERD. Patients who are well maintained on medical therapy have more to lose with surgical intervention than to gain. Nowadays, clear candidates include patients with anatomic abnormalities, large hiatus hernia, or symptoms despite medical therapy, carefully selected patients with extra-esophageal disorders, incomplete response to medical therapy, and persistent plus demonstrable reflux on pH or impedance testing [300]. Careful selection of patients is the key for surgery in GERD. Antireflux surgery may be of benefit in children with confirmed GERD who have failed optimal medical therapy, or who have failed optimal medical therapy, or who are dependent on medical therapy over a long period of time, or who are significantly nonadherent with medical therapy, or who have life-threatening complications of GERD. Children with respiratory complications of GERD are at the highest risk for operative morbidity and operative failure. Before surgery it is essential to rule out non-GERD causes of symptoms and ensure that the diagnosis of chronic-relapsing GERD is firmly established. It is important to provide families with appropriate education and a realistic understanding of the potential complications of surgery, including symptoms recurrence.

Discussion of the Surgical Techniques

In medicine, as in life, time teaches you that nothing is absolute. Therefore no technique is the best and the antireflux operation should be tailored to the child's situation [128].

One has to be very cautious in interpreting the results published, since the groups are different in its percentage of composition [279–325]. The results with the Boix-Ochoa procedure are too good in comparison with other publications; the key is that we are dealing with a group, where only 7 % of the patients are neurologically impaired in contrast with other groups [41, 192]. And the neurologically impaired patient is the most difficult to deal with and has more complications [217, 283].

How I see the problem of choosing a procedure nowadays? It depends on the child's situation, if it is possible to restore the normal physiology or there is a severe damage. In changing the normal physiology and creating a valve, the side effects are greater [76, 330] as happens with the Nissen technique. Inability to burp or vomit and gas bloating are linked to the competence of the valve, and the dumping syndrome perhaps is due to the reduction of the gastric volume related to the operation [301]. But which seemed a disadvantage, it is the clue why Nissen procedures work better than other techniques in the worst cases [58, 198]. Long-term results are excellent, but significant complications and failures do occur, and long-term results are no perfect.

Some authors has described the failures, causes, and feasibility in laparoscopic redo fundoplications (Lopez (2008) Laparoscopic redo fundoplication in children: failure causes and feasibility). Would it be possible to decrease redo fundoplications in the future? The reoperation rate was 18.4 % in the laparoscopic group with maximal esophageal mobilization. It is high than in open fundoplication. Laparoscopic fundoplication in the future must improve the technique in order to achieve the best results and lower redo fundoplications.

The investigations show that fundoplication through the extrinsic compression of the LES

segment by the wrap provides a nadir and basal LES pressure in the absence of the same and a reduction of TLESR due probably to a reduction in the degree of fundic distension [145, 169].

In our experience, the Boix-Ochoa antireflux procedure should be the procedure of choice in the surgical treatment of GER in otherwise normal children, while the Nissen fundoplication is preferable in neurologically impaired children and in patients with GER following esophageal atresia repair [65].

Impedance monitoring can be useful to evaluate the different endoscopic antireflux procedures on the different types of reflux episodes with regard to gas-liquid composition and pH, as well as on volume clearance and the proximal extent of the reflux [67].

The best technique is the operation that gives a solution to the patient, not the surgeon. So GER doesn't need surgery but GERD needs good technical surgery. Discrimination between both GER and GERD is essential.

GERD in Special Situations

GERD and Neurologic Impairment

The most difficult clinical problem in the field of GER is the overall management of the severely neurological impairment (NI) child with persistent vomiting. Vomiting is much more common than in normal children; 15 % of institutionalized, severely retarded children had recurrent vomiting with a frequency of at least eight episodes per month [276]. Three quarters of the vomiting children were shown to have GER. Earlier, such vomiting was largely felt to be psychogenic in origin or simply part of the primary neurologic disease, and little effort was made to critically investigate the cause. Perhaps for this reason, although the vomiting often began early in infancy, diagnosis was usually made relatively late. In those for whom a surgical antireflux procedure was eventually done, the average age at operation was considerably higher than for normal children. Retarded children's representative average and mean ages at operation were 7.5 and 5.9 years, respectively [279, 305].

A number of manifestations or complications of the primary neurologic disease are common. This may both delay the diagnosis of and predispose the child to the development of GER. Vomiting is the most common of these complications, and its misinterpretation is a major factor in delay of diagnosis. Difficulty in feeding and even refusal of feedings are frequent problems in these children, problems not uncommon with GER as well. The vast majority of the NI children are nonverbal; communication and proper identification of symptoms may be exceedingly difficult. A similar proportion also are nonambulatory; therefore, gravity as an aid to esophageal propulsion is not helpful. Increased intra-abdominal pressure also probably plays a role. Scoliosis, spastic quadriplegia, and seizures all are problems in many of these children and all result in periodic elevations of intra-abdominal pressure, enough to overcome the normal antireflux barrier and allow chronic reflux. Severe growth retardation is also common in these children. Complications of GER itself are generally more advanced in NI children than in the normal group. Esophagitis is the most prominent of these. Esophagoscopy has been used as a major diagnostic tool in many reported studies, and esophagitis has been a common finding (66–100 %) [29, 54]. Esophageal stricture, as expected, is frequently identified [325]. Barrett's esophagus, a condition associated with both esophagitis and stricture, also has been found much more commonly in NI than in NN individuals. In one study of institutionalized adults, 26 % had Barrett's esophagus changes on esophagoscopy and biopsy [252]. Another study in children and young adults found a strikingly higher incidence in the mentally retarded group as compared with the normal group [274]. Respiratory problems, particularly repeated episodes of pneumonia, are common and almost always require hospitalization. Various investigators have documented these problems in from 35 % to 85 % of the patients [279–325]. One group of investigators found that 18 % of the children had a history of apneic episodes prior to surgery [280]. Obviously, many of these complications, both of the disease and of GER, are interrelated, and a careful, methodical evaluation is essential when

planning appropriate management. Equally obvious, most of these children have a serious and advanced degree of reflux disease [274].

Quality of life of children with neurological impairment who receive a fundoplication for GERD was improved from baseline in several domains 1 month after surgery [281].

NI had longer lengths of stay and higher mortality rates than did neurologically normal children after antireflux procedures [176].

Diagnostic studies in this group of children are basically the same as in the NN group, but a few modifications are in order. The radiologist, while performing the barium upper gastrointestinal series, must pay particular attention to the possibility of orotracheal aspiration. An antireflux procedure may not be helpful if oropharyngeal aspiration is significant, and, indeed, the problem of aspiration might be worsened. Abnormal esophageal motility is relatively common, perhaps secondary to esophagitis. Hiatus hernia is more often found in NI patients than in the NN group, 51 % in one study [56]. Extended esophageal pH monitoring can be accomplished as a standard method, but in some, the probe is poorly tolerated and may be pulled out at the slightest provocation. Endoscopy with biopsy is helpful as noted previously, because the incidence of esophagitis, stricture, Barrett's esophagus, and hiatus hernia is relatively high [118, 275].

Enteral Feeding in NI with GERD

The provision of adequate nutrition in NI children is often the primary goal. Enteral feedings via a nasogastric tube generally were considered impractical, except as a short-term method in infants with malnutrition secondary to GER. In one study, 12 infants (11 NN) were treated with continuous infusion of formula through a small-caliber nasogastric feeding tube for 11–13 days. Of the 12 infants, 8 had a favorable early response with adequate weight gain and cessation of vomiting [100].

Gastrostomy is the most common long-term solution for enteral feeding. The procedure can be done by a standard Stamm gastrostomy or by the percutaneous endoscopic gastrostomy (PEG) method [113]. The Stamm gastrostomy can be done via a laparotomy or laparoscopically. PEG is a quick and simple technique and has been widely adopted, although it has some unique complications of its own. A substantial number of children without prior clinical evidence of GER develop reflux after a gastrostomy, irrespective of whether the procedure is a Stamm or a PEG [119–322]. About two thirds of children who have normal studies prior to gastrostomy develop GER postoperatively, and about half eventually become symptomatic [175]. Why gastrostomy causes GER remains undetermined; widening the angle of His by pulling down the fundus during the procedure is one possible explanation. Owing to the high incidence of reflux following gastrostomy, routine antireflux operations have been recommended and practiced in a number of pediatric surgical centers. Many, however, feel that all patients referred for feeding gastrostomy should be evaluated for GER and that only those with significant clinical reflux should have a concomitant antireflux procedure. For those who develop clinical reflux postoperatively, the antireflux procedure may be done at that time [146]. Fundoplication after gastrostomy is a much more difficult procedure than fundoplication with gastrostomy.

One should realize that an antireflux operation is not necessarily mandatory in the NI child with reflux whose primary problem is nutrition. Converting bolus gastrostomy feedings to continuous feedings can dramatically resolve vomiting and result in excellent weight gain and markedly diminished pulmonary complications [22]. Another option in NI children who need a feeding gastrostomy and who have minimal to moderate reflux is to place the gastrostomy tube on the lesser curvature, thus fixing the stomach to the posterior right rectus fascia as in a boerema anterior gastropexy. This modification was reported in nine NI children, only two of whom had moderate GER preoperatively. All did well without clinical symptoms of GER and with marked nutritional improvement. Postoperative barium studies in eight did not show reflux [28, 285].

Still another approach in these children is to use a jejunostomy. By one technique, a percutaneous gastrostomy is established under fluoroscopic

control while a small plastic tube is threaded through the gastrostomy tube and guided into the jejunum. Comparison of this technique with a Nissen fundoplication showed a strikingly lower incidence of complications in the former [3]. Obviously, this same principle could be achieved by passing the jejunal tube through a preexisting gastrostomy. One annoying problem in such methods is occasional displacement of the feeding jejunal tube upward into the stomach and the necessity for its replacement under fluoroscopic control. This technique does not directly treat the GER, and medical management must be continued. A final method along these same lines is a Roux-en-Y jejunostomy for feeding. A gastrostomy for decompression is done at the same time if one is not already in place [78]. This procedure obviously is more complex, but the results in a small series have been excellent in terms of improved nutritional status and dramatic decrease in GER symptoms.

Antireflux Surgery in NI

The exact percentage of NI children without demonstrable GER who receive an antireflux procedure in conjunction with a feeding gastrostomy is difficult to determine, but in one series the indication for the antireflux operation was prophylactic in 30 % [213, 272].

All of the various antireflux surgical procedures have been used in NI children. The Nissen has been most often used, as with NN children, but the Thal operation has also been used almost exclusively in some series [245, 297]. The most vexing problem with these children is the high rate of both postoperative complications and deaths within the perioperative period as compared with NN children undergoing the same procedures. One series noted an early complication rate of 11 % and a late complication rate of 26 % [236]. All but one of the early complications were small bowel obstructions; more than half of the later complications were wrap herniations or wrap failure. NN children from this same institution had one third the number of early complications and less than half the rate of late complications. Reoperation for late complications was required in 19 %. The Nissen fundoplication was used in about 80 % of the NI children, and Thals in the remainder. Another series reported on 35 profoundly disabled children who had antireflux procedures, almost all of which were Nissens [272]. The results of the anterior gastropexy of Boerema in 50 NI children were similar: 25 early and 9 late complications, 17 reoperations, and 2 deaths related to the operation [41]. A still larger series reported distressingly high complication rates following Nissens in 193 patients [192]. Both of the fundoplication authors questioned the advisability of continuing with operations that were designed to improve the quality of life in these children but that were plagued with numerous problems.

Experience using the Thal operation suggests a more optimistic picture with an 8 % failure rate and an 11 % complication rate [297]. The complication rate is about the same as with the NN children, but the failure rate in the NN is only 2 %. In a series of Thal procedures in 141 NI children, recurrent GER or recurrent hiatal hernia required reoperation in 10 % [245]. Only 6 % required a later pyloroplasty due to DGE for symptoms of gagging and retching.

It is more than apparent that antireflux operations in NI children carry a considerably higher risk than in otherwise normal children. However, in all the series cited, most of the children were much improved, and parents and other caregivers expressed a high degree of satisfaction with the outcome. In a study that examined this important issue, feeding indices were improved and the child's comfort and quality of life were perceived to be significantly better [217]. Furthermore, the level of frustration in caring for the child was less and the quality of life for the parents as well as for the child was improved.

Esophageal Atresia and GER

GER following repair of esophageal atresia malformations is common. The frequency is difficult

to establish precisely, but significant reflux occurs in at least 50 % of these babies [76–96]. In cases of isolated esophageal atresia (no tracheoesophageal fistula [TEF]), the incidence of GER following primary repair was 100 % in a series of nine infants [183].

The cause of the GER has been assumed by many to be secondary to the repair of the esophageal atresia itself. Tension on the anastomosis with upward displacement of the lower esophageal segment may shorten the intra-abdominal esophagus and widen the angle of His. Dissection of the TEF and the lower esophageal segment may damage the vagal innervation, or scarring secondary to the dissection may have the same effect. In fact, a study of 25 such children revealed that excessive tension at the anastomosis was the only factor studied that was associated with an increased incidence of GER [152]. However, most investigators in the field now believe that the cause is a primary, probably congenital, defect in the motor function of the distal esophagus [227]. Esophageal dysmotility, aperistalsis, nonprogressive contractions with low amplitude, and disorganized contractions all have been observed. The lack of distal esophageal contractions is well documented and the key of GERD after repair of esophageal atresia [169]. The long-term follow-up of 22 adolescents or young adults who had repair of esophageal atresia and distal TEF as newborns examined some of these problems [295]. The technique used was a combination of 24-h esophageal manometry and pH monitoring on an ambulatory basis. Half had a pattern of long nocturnal episodes of reflux with very slow clearance. All had markedly diminished esophageal contractibility, disorganized propulsive activity, and absence of acid-clearing capacity. Propulsion of ingested fluids and solids and clearance of refluxed fluids were accomplished largely by gravity. GER was noted in more than half of these patients, so that it is clear that the reflux noted early in life in these children persists indefinitely.

The clinical manifestations of reflux are similar to normal children with GER. Respiratory symptoms, such as recurrent pneumonia, are common, and life-threatening episodes of apnea or cyanosis may occur [96, 234]. Failure to thrive due to recurrent vomiting, dysphagia, and esophagitis is often a problem. The esophageal anastomosis may become tight, and the stricture often does not respond to dilation, presumably due to the frequent reflux of acid fluid. Esophagitis is particularly common.

Conventional medical treatment is effective in about half of the children. This includes upright positioning and thickening of the feedings. Owing to dysphagia, supplemental gastrostomy feedings may be necessary. Infusion gastrostomy feedings are probably more effective than bolus because less vomiting results. Omeprazole is helpful for this infants because esophagitis and persistent strictures are common.

When medical measures are not effective and complications such as failure to thrive, apneic spells, recurrent pneumonia, or anastomotic strictures persist, some form of antireflux surgical procedure is necessary. Many reports document excellent results. But postoperative long-term follow-up until the patients reach adulthood is absolutely necessary to ensure that development of a Barrett's esophagus is not overlooked [135].

Fifteen infants with tight anastomotic strictures failing to respond to repeated dilations were reported [241]. The cause was felt to be frequent episodes of reflux, and all were managed by an antireflux operation. The stenoses were cured in all. Another group of children was reported to have excellent but slightly less spectacular relief of stricture, vomiting, pneumonia, and dysphagia [108]. Nissen fundoplications were performed in all nine with no major complications and with relief of their reflux symptoms in all. Respiratory problems were markedly diminished and the strictures were successfully managed. Surgical treatment of reflux in this group of children has been uniformly successful. The experience with fundoplications used in 14 children with GER following repair of esophageal atresia and TEF was reported to be

distressing [74]. All had competent fundoplications on follow-up study, but all also had absent esophageal peristalsis below the anastomosis. Another report relates similar problems using Nissen fundoplications in this scenario [324]. The investigators felt that the dysphagia was secondary to the inability of the defective distal esophageal motility to overcome the increased resistance of the fundoplication.

What appeared to be excellent short-term results proved to be poor long-term results with fundoplications in another report [183]. In other reports, the problems are not as severe. Reoperation was required in 18 % of those children with a Nissen fundoplication and in 15 % of patients who had a Thal fundoplication following esophageal atresia/TEF repair [182, 275]. Reoperation rates, of course, do indicate failure but do not necessarily reflect the total incidence of morbidity following antireflux surgery.

Achalasia and GERD

Patients with achalasia are at increased risk for chronic GERD, esophagitis, and Barrett's esophagus following treatment by either pneumatic dilatation or myotomy. The benefit of antireflux therapy at the time of myotomy remains controversial. All the patients with a history of achalasia or history of esophageal atresia repair require follow-up for possible complications of GERD.

Chronic Respiratory Disorders

Intraesophageal pH studies in children with chronic respiratory disorders detect a much higher prevalence of pathologic GER reflux, but is silent in the majority. Bronchopulmonary dysplasia, a chronic lung disease of infancy with varying degrees of alveolar growth arrest, airway branching abnormalities, and peribronchiolar fibrosis, has been associated with GERD.

Lung Transplantation

Severe GERD is common in patients presenting for transplantation, and high incidence of GERD occurs following lung transplantation in children and adults. Complications of GERD are a common source of morbidity in patients with transplantation. Pneumonectomy seems to contribute to esophageal and gastric motor dysfunction. It has been suggested that in the allograft lung, nonimmune-mediated injury because of reflux contributes to the development of bronchiolitis obliterans syndrome [204].

Consequences for Young Adults

In about 4 % esophageal strictures will develop and 5 % will die because inanition or pulmonary infection [59]. Potentially serious consequences are esophageal stricture and Barrett's esophagus.

The treatment of esophageal stricture secondary to esophagitis has changed little in the past 30 years [216]. Esophagoscopy is essential initially to demonstrate the type and extent of the lesion and the possibility of dilatation. Dilatations are then initiated. If the stricture is particularly tight or long, a gastrostomy will be necessary not only for alimentation but also for the placement of an indwelling string to permit retrograde dilatations. Even with improvement from dilatations, some form of antireflux operation is necessary; and dilatations may need to be continued postoperatively for some time [34]. Rarely the stricture is limited to a short segment which allows for resection and anastomosis. If the stricture is long and unyielding, esophageal replacement occasionally may be required, either by gastric tube or colon replacement. Better knowledge of the consequences of GER and its pathophysiology, earlier diagnosis, and effective therapy account for the fact that strictures from reflux esophagitis are now seen less frequently than in past decades. Why strictures develop in some patients but not in others remains an unanswered question. The answer

may well be found in variability of the mucosal defense mechanisms and the noxiousness of the refluxate.

In the last years our group is treating the severe strictures with "autoexpanding" prosthesis, with excellent result, lower morbidity, longer time between dilatations, family and child satisfaction, and a high percentage of full success [49, 50].

A large number of reports confirm the effectiveness of omeprazole in the treatment of esophagitis in children [80–132]. The drug has an important role as an adjunct in managing reflux strictures. Although its effectiveness in esophagitis is apparent, its success in truly advanced esophagitis is not as impressive; less than half of grade 4 esophagitis healed with omeprazole. Recurrence seems to be inevitable when the drug is stopped.

Barrett's esophagus is a complication of esophagitis and is often accompanied by stricture [42]. Although usually regarded as quite uncommon in childhood, the incidence has been reported at 4 % and 14 % of children with GER in two series. In another report, Barrett's esophagus was found in 25 % of the children with reflux strictures. In adults, progressive increase in the incidence and severity of dysplasia in the columnar epithelium has been documented on repeated endoscopic and biopsy observations over a period of years [251].

The progressive increase in the incidence and severity of dysplasia, together with the development of carcinoma, makes Barrett's esophagus most worrisome [134]. Two cases of carcinoma arising in Barrett's esophagus in children were reported from one institution [2]. One patient was 11 and the other 14 years of age at diagnosis of the malignancy. There is a report of an esophageal adenocarcinoma located adjacent to the esophagogastric junction in a 20-year-old woman who had repair of esophageal atresia and TEF as a newborn [125]. She was managed by an extensive resection with restoration of continuity by a colon segment interposition. The specimen did not show Barrett's epithelium, but certainly there is a reasonable possibility that Barrett's esophagus was, in fact, present at one time but was obliterated by the tumor.

How to best handle the child with reflux and Barrett's esophagus is obviously a major problem. One child, 12 years of age, was treated by antireflux operation with an excellent clinical result. Two years later, on both gross endoscopic examination and histologic review, there was distinct evidence of regression with replacement of the columnar epithelium by squamous epithelium, and this regression continued over a further 3-year period. In another case, complete regression followed antireflux surgery [63].

Generally, however, Barrett's esophagus in childhood does not regress after antireflux surgery. Prolonged follow-up evaluation with endoscopy and biopsy is recommended if dysplastic changes are to be found and carcinoma either can be prevented or found at an early stage [261]. The use of endoscopic laser ablation of the epithelium has been reported [103, 130].

Other questions related are about the risk of esophageal adenocarcinoma after antireflux surgery. Is it able to prevent later development of adenocarcinoma? Follow-up evaluation study for cancer incidence in the antireflux surgery group in Swedish population showed antireflux surgery cannot be considered to prevent the development of esophageal or cardia adenocarcinoma among persons with reflux [174].

Experimental models of duodenogastroesophageal reflux have studied the effect of ingestion of sodium nitrite solution on the genesis of adenocarcinoma and have described the important role of nitrites in the genesis of adenocarcinoma associated with Barrett's esophagus [203].

GERD is associated with allograft dysfunction after lung transplantation. Patients with symptomatic GERD demonstrated an increased incidence of bronchiolitis obliterans syndrome. So more sensitive and specific diagnostic tools should be implemented in all lung transplantation recipients to investigate the impact of symptomatic and silent GERD and thus improve outcomes after lung transplantation [204].

Where the Emphasis Is Likely to Lie in the Future

GERD is one of the most common health problems, and it affects more than 50 % of the world's population.

The use of the laparoscopic approach to perform antireflux procedures has increased since its introduction in 1991 but the goal in the future will be to identify the risks and benefits of laparoscopic antireflux procedures [161].

When it is possible, laparoscopic fundoplication is the preferred surgical option. And laparoscopic redo Nissen fundoplication for a failed antireflux procedure is safe and effective for some authors [255]. But laparoscopy procedure has several limitations: two-dimensional imaging, restricted instrumentation motion, and ocular fatigue and headaches in surgeons. Also haptic feedback (force and tactile), natural hand-eye coordination, and dexterity are not necessary. The physiologic tremors of the surgeon are readily transmitted through the length of rigid instruments. This limitations make more delicate dissections difficult and it is because some techniques like Boix-Ochoa antireflux procedure are more difficult by laparoscopy than in open surgery.

During the last few years, minimally invasive robot-assisted surgery has continued to expand into different surgical procedures. The benefits include three-dimensional images, which allow surgeons' superior visibility. Also the robotic system has a 360° range of motion, maintains steadiness, and has surgical tools with greater degrees of freedom. Since the first report of robot-assisted fundoplication (RAF) published in 1997, computer-assisted fundoplication has become increasing [8, 131, 196]. But controversy remains. Is it a promising technical innovation [207, 329] or does it just add time and increase the cost [92, 178, 206, 209, 237]?

The answer is still unclear but probably in the next years there will be more information about this problem. Some authors don't find significant differences in outcome and there are no clear benefits of using Nissen fundoplication as a robotic-assisted versus laparoscopic procedure in children [4, 208].

RAF is one of the latest approaches in the evolution of endoscopic surgery also in pediatrics. Perhaps in the future with the development of new instruments, better positioning, an independent optical command system, especially adapted tools for digestive surgery, tactile sensitivity, and force feedback, complex surgical procedures will be performed easily and accurately. And obviously the operation times will be decreased, and the costs may decrease as well as surgical complications [195].

In the future there will be new developments in esophageal surgery: long-term outcomes after laparoscopic antireflux surgery, the use of surgically placed implantable device for LES augmentation (Linx), the use of mesh for hiatal hernioplasty, and prone and nonthoracic approaches to minimally invasive esophagectomy [273]. But the indications must remain identical for open and laparoscopic procedures [296].

What would be the endoluminal therapy role in robotics era [110]? There are not enough scientific and clinical data on safety, efficacy, and durability to support the use of endoluminal therapies for GERD in routine clinical practice for some authors. But controversy is still alive for others [313].

Several endoscopic antireflux techniques have been developed to enhance the function of the lower esophageal sphincter or alter the structure of the angle of His with the goal of recreating or augmenting the reflux barrier. Many methods are no longer available, and some await regulatory approval [311].

What are the risk factors for recurrent gastroesophageal reflux disease after fundoplication in pediatric patients? Would we be able to reduce the redo procedures in the future [212]? Factors associated with increased risk of redo GERD are age of less than 6 years, preoperative hiatal hernia, postoperative retching, and postoperative esophageal dilatation.

What would be the best way to evaluate the results of surgical therapy for gastroesophageal

reflux disease? Some authors have performed pH monitoring and esophageal manometry in this evaluation and have concluded that Nissen fundoplication is effective for the treatment of GERD and didn't affect esophageal motility but this procedure decreases in contraction time.

Impedance testing is useful in the management of GERD [27].

Not to all obviously, new answers will generate new questions about GERD [249, 268].

Conclusion

We have to recognize that nowadays some of the mysteries of GER lies in the brain stem and the vagal control of the esophagogastric junction and once again we are in the threshold of a new era and the most encouraging fact for the investigator is that the sphincter is like a sphinx that gives up its secrets grudgingly, so we must continue to investigate, because today's knowledge is not tomorrow's truth and there is nothing as permanent as change.

Following other paths and achieving novel findings all around, the pathophysiology of esophageal inflammation should enhance our understanding of GERD and its complications and provide new treatment insights. The complex process involving multifaceted inflammatory mechanisms, expression of inflammatory mediators in GERD, and their potential cellular sources is a new field in knowledge. What is the contribution of inflammatory mediators to complications of GERD, motility abnormalities, fibrosis, and carcinogenesis [250]?

We would however stress that conservative treatment should be thought of first, as it is impossible to improve an already healthy child by surgery.

The pathophysiology of GERD involves contact of the esophageal epithelium with acid/pepsin in the refluxate. For this contact to occur with sufficient duration, there must be a combination of defects in antireflux and luminal clearance mechanisms for acid/pepsin to overwhelm an intact epithelium or defects within the epithelium develop that subsequently enable normal acid contact times to become damaging to the epithelium.

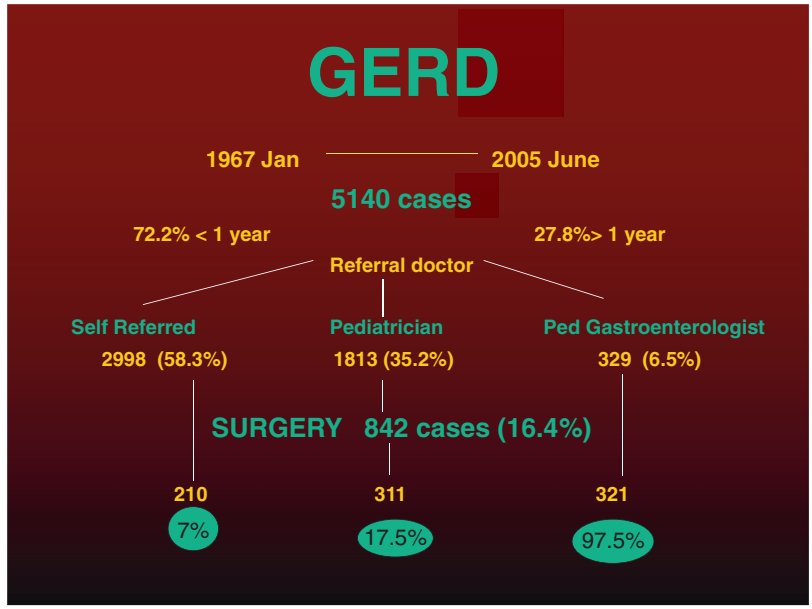
Two methods directly measure fluid flow: [1] scintigraphy, which directly measures radiolabeled liquid gastric contents flowing into the esophagus and [2] MII, a new method that recognizes the flow of gastric contents into the esophagus by detecting impedance falls from a high (esophageal mucosa) to low (gastric contents) value across electrode pairs placed throughout the esophagus; MII can also distinguish liquid from gas refluxant [163, 270, 302, 314].

PPIs are recommended as initial therapy in children with erosive esophagitis. Initial treatment for 3 months is advised. If adequate control of symptoms is not achieved within 4 weeks, the dose of PPI can be increased. Most patients require only 1-day dose of PPI to obtain symptomatic relief and heal esophagitis [101]. The optimum dosage regimen is to administer a once-daily dose 15–30 min before the first meal of the day. PPIs should not be stopped abruptly, because rebound acid secretion may cause recurrence of symptoms. PPI should be tapered for at least 4 weeks.

Before surgery it is essential to rule out non-GERD causes of symptoms and ensure that the diagnosis of chronic-relapsing GERD is firmly established.

After Boix-Ochoa experience on 5,140 children, some of them with more than 30-year follow-up, under 3 years of age with GERD 3,711 under 1 year and 1,429 over 13 months with surgical treatment of 16,4 % of them, the conclusion is the highest % of patients with lowest surgical treatment where patients self-referred (7 % surgery) or referred by pediatricians (17.3 % operated) and the highest rate of surgically treated patients is logically referred by pediatric (Table 91.7) gastroenterologists (97,5%). Where is the border between medical treatment and surgery? Which kind of medical treatment and how

Table 91.7 Gastroesophageal reflux disease



long and when patients begin to be a surgical patient? Our experience shows that patients, who consult a surgeon earlier, have better results, than patients that are being managed long time by medical treatment only. We hypothesize "early GERD surgical treatment" as the best treatment for the patient against long medical treatment that reduces GERD but don't heal.

Careful selection of patients is the key for best results in GERD surgery.

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The Spectrum of Surgical Anti-reflux Procedures: Which Operations Work?

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E.M. Kiely

Introduction

Most of the underlying pathophysiology of gastro-oesophageal reflux (GER) has been elucidated in adults. The underlying mechanism giving rise to reflux is transient relaxation of the lower oesophageal sphincter (TRLES). This is combined with relaxation of the diaphragmatic crura and also with oesophageal shortening [1, 2].

The same mechanisms have been shown to occur in the paediatric age group, both in neurologically normal (NN) and neurologically impaired (NI) children with GER [3]. The cause of the sphincter relaxation has not been established, but is considered to be partly related to gastric distension [4].

Nonoperative treatment is directed at lessening the damage produced by acid and pepsin digestion of oesophageal mucosa as well as reducing the supra-oesophageal effects on airways, lungs and dentition.

The underlying pathology is unaffected by medical treatment. Surgical therapy appears to affect the behaviour of the lower oesophageal sphincter (LES), and the reasons for this are unclear at present [5].

Common presenting symptoms include pain, vomiting, failure to thrive, respiratory complications and the consequences of oesophagitis [6].

The spectrum of associated conditions in children is greater than that found in adult practice. A number of structural abnormalities predispose to reflux – oesophageal atresia (EA) and congenital hiatus hernia. The respiratory consequences of reflux include apparent life-threatening events (ALTEs) in infants, secondary chest infections, asthma and bronchiectasis in older children. NI children frequently have pathological reflux resulting in pain and haematemesis. A group of children exist where severe oesophagitis, haematemesis and structuring present early, and finally a group of normal children may present with no structural problems, but for whom GER produces troublesome symptoms.

The aspects of diagnosis have been dealt with above. Before contemplating surgical management of GER, an upper gastrointestinal study is mandatory both to define the anatomy and to give some information on the presence or absence of reflux. Depending on the X-ray findings, oesophagoscopy may be considered appropriate. Surgery is undertaken when medical treatment fails or is unsatisfactory. Children may have many decades of life ahead of them, and a lifetime of medication may be the alternative to an operation. There are no data on the safety of decade-long treatment

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with proton pump inhibitors (PPIs). There is also a concern about the development of Barrett's oesophagus if GER continues indefinitely.

Unfortunately, the results of operation are not predictable, although the great majority of children are considered to have a good outcome from surgery [7]. It is also clear that outcomes from surgery differ among different patient groups. NI patients and those *with repaired* EA, for instance, do less well than NN children [8, 9]. Finally, there are no very long-term (>15 years) results of surgery available.

Indications for Operation

Surgery is generally performed for intractable symptoms, unresponsive to medical treatment. In prematures with chronic lung disease, discontinuation of ventilation may be delayed or impossible because of reflux and aspiration. In addition, repeated chest infections may worsen ongoing lung damage. Apparent life-threatening events (ALTEs) and apnoeas may be associated with reflux in young infants. These may be abolished by successful anti-reflux surgery. Vomiting and failure to thrive are features of severe reflux in infancy. The nonoperative management of these problems is dealt with above but if weight gain remains poor, surgery may be the sole option.

Respiratory complications in older children include recurrent chest infections, asthma and bronchiectasis. Pathological reflux is also common in cystic fibrosis. When reflux is confirmed in these children, a trial of full anti-reflux treatment is undertaken but if significant symptoms persist, surgery should be considered.

Severe oesophagitis – ulceration and stricturing – is uncommon in children. Long-term relief of symptoms is possible with continued anti-reflux treatment. Stricturing usually responds well to fundoplication.

Severe reflux is common in NI children [10]. Up to 70% may be affected. Symptoms include pain, irritability, vomiting, haematemesis, recurrent chest infections and poor weight gain. All of these symptoms may be seen in the same patient over time.

Many of these children will already have a gastrostomy in place because of unsafe swallowing. The later development of pathological reflux suggests a progressive foregut dysmotility, and abolishing reflux by surgery may transform the child's life.

Uncommon indications for anti-reflux surgery include those undergoing major airway reconstruction and those who have had lung transplantation. In the former group, continued reflux may jeopardise the repair and, in the latter group, compromise lung function.

Reflux in older children and adolescents often presents as effortless regurgitation, halitosis, dental erosion and pain. When symptoms persist over years and are not completely abolished by medical treatment, surgery may be requested.

Surgery is the sole means of repairing a hiatus hernia. While minor degrees of hiatus hernia may not mandate operation, major degrees of herniation will do so.

Available Operations

At the present time, fundoplication is the favoured anti-reflux operation. Most perform the 360° Nissen fundoplication and a minority the various forms of incomplete wrap – Thal, Toupet and Boix Ochoa. The type of procedure performed depends mainly on surgical preference, and there is a paucity of literature comparing one with the other. A recent prospective randomised trial from Oxford in the UK suggests that the Nissen fundoplication compared to the Thal, across a broad range of children with co-morbidities, produced better results [11]. Nonetheless, many prefer to use an incomplete wrap when oesophageal motility is considered markedly abnormal.

In the era of minimally invasive surgery, none now argue that open operation is preferable if the same procedure can be done without the trauma of access. Laparoscopic fundoplication is now considered the standard of care [12]. The relative ease of performance of the Nissen operation has probably deterred many from wishing to undertake any of the incomplete wraps. The Nissen can

be completed with perhaps three sutures, and the alternative operations need many more.

Up to now, the standard approach in performing a fundoplication has been to divide the phreno-oesophageal ligament and fully dissect the oesophagus from the pleura and mediastinal structures. As St. Peter et al. pointed out [13], this is a replication of adult practice. Wrap herniation is a significant post-operative problem in children, and minimal mobilisation may reduce this problem to a marked degree. In this paper, the instance of post-operative hiatus hernia was reduced from 30 % to 7.8 % [13]. This approach is not possible in all, but most children with reflux do not have a hiatus hernia and, consequently, can have the procedure performed with very little mobilisation.

It is unclear if division of the short gastric vessels is beneficial or not. Published reports and our own experience suggest that a floppy wrap is possible for most without dividing these vessels. In some, the wrap cannot be performed without the release of at least the upper short gastric vessels. The experience of Esposito et al. [14] is probably representative – they divided the vessels in 6 (2.5 %) of 300 patients undergoing fundoplication. This pragmatic approach has much to recommend it. Others divide the vessels as a routine [13].

There is no agreement either on the need for an oesophageal bougie during construction of the wrap. Many authors use a bougie sufficient to fill the oesophagus at the time of operation [15]. There are no studies to demonstrate that this is necessary or that it reduces the chances of forming a wrap which is too tight.

There is also no clear advice on when to perform a gastric drainage procedure. It is clear that gastric drainage is abnormal in some at the time of diagnosis. Delayed or accelerated gastric drainage may become problematic many months after successful fundoplication. Some authors recommend radionuclide scans in NI children as part of the diagnostic workup and perform pyloroplasty if the result is abnormal [16].

Oesophagogastric disconnection (OGD), described by Bianchi [17], is mainly reserved for NI children who are incapable of feeding orally and who are gastrostomy dependent. The oesophagogastric junction is divided, the stomach closed, and a Roux loop of the jejunum brought up and anastomosed to the oesophagus. This allows the child to swallow saliva and some food if possible, but the bulk of calories is delivered by gastrostomy.

Some authors use this as the primary procedure in NI children, but others only when the first or second fundoplication has failed [18, 19]. This operation is not widely used as a primary procedure but continues to be of use in a minority of patients after a failed fundoplication.

The Collis gastroplasty to gain length is used when oesophageal length is problematic [20]. This is a particular problem when managing children after repair of pure oesophageal atresia. It is clear from the published literature that this operation may succeed where the previous fundoplications have failed [21, 22]. However, as the tubularised stomach produces acid and pepsin, the distal oesophagus will suffer from acid reflux indefinitely. The effects of this are uncertain and concerning. It is not clear if Barrett's oesophagus will inevitably result in these children.

The various endoluminal techniques are addressed below.

Results of Surgery

The reported results of anti-reflux surgery present widely differing outcomes, both in terms of success, complications and also in regard to the need for repeat surgery. Many of these differences are related to differing patient populations and in particular to the number of NI children undergoing surgery. In addition, prospective series give different results from retrospective reviews and are in a minority.

Perioperative complications including visceral perforation, haemorrhage and splenic injury are reported in all the large series. These occur after open or closed surgery and rates of 5–10 % are common [8, 14]. Occasional children are unable to tolerate the pneumoperitoneum because of chronic lung disease, congenital heart disease or severe spasticity.

Dysphagia is the commonest early postoperative problem and is usually managed by dilatation of the wrap. A recent report noted an incidence of 23 % dysphagia after fundoplication, and, in most of these children, the dysphagia resolved without intervention [23]. Four percent of the total needed dilatation and 2 % revision of the wrap.

The report dealing with the advisability of oesophageal mobilisation noted that 8.5 % of patients who had undergone extensive mobilisation needed dilatation of the wrap versus 0 % of those who had minimal dissection at the hiatus [13]. Severe dysphagia may be more common after a Nissen than a Thal fundoplication [11].

Recurrence of symptoms ascribed to reflux is common in NI children. Strecker-McGraw et al. [24] reported recurrent symptoms within 3 months of surgery in 3.6 % of their patients. One-third of these had reflux confirmed on pH study.

With longer-term follow-up, 71 % developed troublesome symptoms, and recurrent reflux was again confirmed in one-third [25]. This latter report dealt with the management of NI children only.

Gas bloat is more likely as a complication of Nissen than Thal complications. The incidence varies and may not be influenced by neurological impairment. Mathei et al. [23] reported gas bloat as a significant problem in 15 % with spontaneous resolution in all. Kimber et al. [26] noted an incidence of intractable gas bloat needing revision surgery in 10.6 %, all of whom had undergone a Nissen fundoplication.

Adhesion obstruction has been a problem after open operation. Rates of about 3–8 % have been reported [7, 25]. This is rarely seen as a complication after laparoscopic anti-reflux surgery.

The distressing symptom complex of choking – gagging – retching is familiar to all surgeons who deal with NI children. Smith et al. [8] note that this was present in 11 % of their patients prior to surgery and in 23 % after operation. Similarly, Martinez et al. [25] note an overall incidence in NI children of 13 % pre-op and 29 % postoperatively.

Despite all these potential complications, the results of anti-reflux surgery are considered good. In a multicentre review of over 7,000 patients, good results were obtained in 95 % of NN children and in 84.6 % of NI children [7].

Reoperation is considered the main criterion of failure. It is clear that fundoplication is a very successful operation in NN children who have no serious co-morbidities. Esposito et al. [14] reported a repeat operation rate of 2.5 % in 300 NN children undergoing laparoscopic Nissen, Toupet or Thal procedures in three different hospitals.

In the prospective study by Kubiak et al. [11], the overall failure rate was 5.9 % for Nissen fundoplication and 15.9 % for Thal fundoplication. All but one child who needed repeat surgery was neurologically impaired.

A high failure rate is also reported in children who have undergone repair of oesophageal atresia. The report from Ann Arbor in 1993 probably reflects widespread experience – a failure rate of 33 % after Nissen fundoplication, compared to a 10 % failure rate in the remainder of non-oesophageal atresia patients [9]. In addition, there were three deaths in this series from complications related to the anti-reflux operation.

A similar report from Toronto and Washington in 1998 noted a 25 % failure rate in this group of patients [27]. The only NN patients who needed repeat surgery were patients with repaired oesophageal atresia.

The case against anti-reflux surgery has been made quite cogently by Hassall [28]. Using undefined criteria for surgery other than an apparent determination not to refer children for operation, the rate of fundoplication had been reduced from 40 to 50 operations per year down to four to five operations per year in the British Columbia Children's Hospital. It is not clear whether or not the unoperated children with reflux were better or worse off. Tellingly, in the clinical vignette used to demonstrate dilemmas of management, the fundoplication which had been performed subsequently failed.

Prospective randomised studies of medical versus surgical therapy in children have not been performed to date. The same criticism cannot be maced for adult practice. A Swedish study with 5-year follow-up compared the two modes of treatment and found surgery to be superior to

omeprazole [29]. When the dose of omeprazole was increased, the superiority of surgery did not reach statistical significance.

A long-term study from the Veterans Administration in the United States [30] described the outcome of medical versus surgical therapy with 10 years follow-up. Sixty-two percent of the surgical patients were again taking anti-reflux medication but their symptoms of gastro-oesophageal reflux were significantly less than the non-operated group. An unexplained finding in this study was an excess mortality in the surgical group from cardiovascular diseases. This was an unexpected finding and was unexplained.

A systematic review of six randomised trials and three cohort studies comparing anti-reflux surgery with medication showed consistently superior results in the surgical groups [31]. In three of the studies examined, the medical therapy was a PPI and the results of surgery remained superior.

A caregiver's assessment of surgical results in NI children was reported in 1996 [32]. The results showed improvement over a wide range of questions which included ease of feeding, ease of caring and comfort of the child.

The results of the oesophagogastric disconnection have not been studied or reported in the same numbers. A small prospective study enroled 26 patients and compared Nissen fundoplication and disconnection [18]. The follow-up was short – 12 months – but the disconnection patients were considered to have a better outcome across a broad range of assessments. These included weight, haematocrit, feeding time and the results of a parental questionnaire. Similar results were reported from the Alder Hey Hospital in Liverpool [19] and from a caregiver's perspective in Manchester [33]. All of these reports described the results in NI children.

At the present time, therefore, anti-reflux surgery in the form of fundoplication is successful in most children. The Nissen operation is the most popular and probably the most effective. The main complications are the significant failure rate and the introduction of new symptoms after surgery. Patients with NI have a much worse outcome after surgery, and repeat fundoplication carries a failure rate in the region of 40 % [34].

The surgeon who is called upon to operate should be very clear of the possible outcomes of surgery. Appropriate advice may then be given to the parents such that the correct decision for the individual child is made.

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Fundoplication in Infants and Children

93

Oliver J. Muensterer

Introduction

Gastroesophageal reflux is a physiologic phenomenon in infancy before the lower esophageal sphincter matures. In otherwise healthy infants, it rarely causes more than an inconvenience for the caregivers in the form of frequent spit-ups after feeds. As long as the child is thriving and otherwise asymptomatic, no specific treatment is necessary. When gastroesophageal reflux is severe enough to compromise normal growth, cause respiratory symptoms, or lead to inflammation of the esophagus, treatment is indicated. Nonoperative therapies such as thickened feeds, promotility agents, H2-receptor blockers, proton pump inhibitors, or elevating the head of the bed were all found to have only marginal benefit in the treatment of gastroesophageal reflux in young children [1–3]. Complications of untreated pathologic gastroesophageal reflux include failure to thrive, respiratory compromise, and esophageal peptic strictures [4].

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There are three physiologic mechanisms to prevent gastroesophageal reflux in humans (Fig. 93.1). First, the lower esophageal sphincter (LES) is a concentration of circular muscle fibers at the lower end of the esophagus proximal to the gastric cardia [5]. The LES is a dynamic barrier that relaxes at the end of an esophageal peristaltic wave to allow a food bolus to pass into the stomach. At other times, it maintains a certain resting tone to prevent gastric content to backflow into the esophagus. Second, the esophagus joins the stomach at a sharp angle, the angle of His [6]. This angle acts as a one-way valve, allowing food to pass from the esophagus into the stomach, but closing when the fundus of the stomach is distended. A corresponding mechanism is found in other organ systems such as the urinary tract, in which vesicoureteral reflux is avoided by the ureter entering the bladder at a physiologic angle. Finally, the most distal portion of the esophagus is normally located within the abdominal cavity. This decreases the pressure gradient across the gastroesophageal junction, because the pliable wall of the esophagus transmits the ambient pressure to its lumen. Thereby, the physiologic pressure gradient between the abdominal and the thoracic compartment is not applied to the gastroesophageal junction, but proximal where it cannot exacerbate gastroesophageal reflux. All surgical fundoplication procedures aim to favorably influence the factors above.

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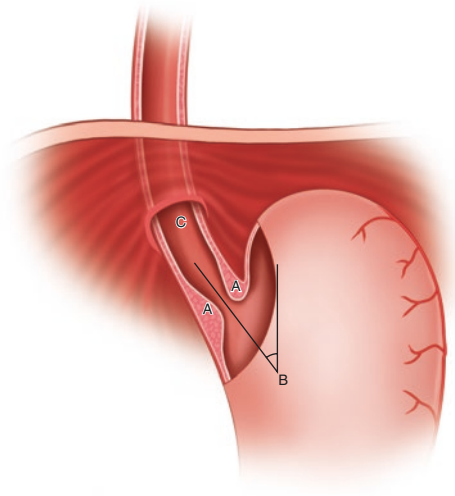

Fig. 93.1 Physiologic and anatomic anti-reflux mechanisms. The lower esophageal sphincter (*A*) is a dynamic concentration of circular muscle that usually remains closed in the resting state but opens up at the end of a peristaltic wave. The normal esophagus joins the stomach at a sharp angle, the angle of His (*B*), creating a vale-like configuration. Usually, the most caudal portion of esophagus is located in the abdomen (*C*), lowering the pressure gradient across the gastroesophageal junction due to the pliable nature of the esophagus

The first surgical intervention for gastroesophageal reflux was the hiatal hernia repair described by Allison in Leeds, England, in 1943 [7]. The recurrence rate was high, prompting the development of many different techniques of actual fundoplication over the following decades. Nissen's first fundoplication was performed in 1937 while he was the chief of surgery in Istanbul to reinforce the esophageal anastomosis he performed after resecting an ulcer [8]. Only later was this technique adapted for the actual treatment of gastroesophageal reflux disease and published by Nissen in 1956 [9]. Toupet described the posterior fundoplication in 1963 [10], and Thal proposed an anterior fundoplication in 1968 [11], to mention only the most popular procedures currently performed in children.

In 1991, the first laparoscopic fundoplication in adults was described by Dallemagne in Liege, Belgium [12]. Georgeson in Birmingham, Alabama, and Lobe in Memphis, Tennessee, published the first series of pediatric laparoscopic Nissen fundoplication independently in 1993 [13, 14].

This chapter describes the indications, techniques, and outcomes of fundoplication for the treatment of gastroesophageal reflux disease in children.

Indications for Fundoplication

As mentioned above, the main indications for a fundoplication in children are emesis of enteral feedings precluding the ability to thrive, aspiration of refluxed gastric content into the airways, persistent inflammation of the esophagus despite medical management, peptic stricture, and apparent life-threatening events found to be correlating with gastroesophageal reflux episodes.

Several patient groups have been shown to be at higher risk of gastroesophageal reflux. Based on the clinical presentation, some authors recommend early fundoplication in these children. For example, up to 80 % of patients who underwent esophageal atresia repair are at risk of developing symptomatic gastroesophageal reflux [15]. Therefore, the pediatric surgeon's threshold for performing a fundoplication in such patient may be lower, particularly because prophylactic proton pump inhibitors have not been shown to reduce stricture formation [16].

Patients with congenital diaphragmatic hernia are another target group in this regard. In one study, congenital diaphragmatic hernia (CDH) patients with an intrathoracic liver and patch repair had shorter postoperative hospitalization times and lower incidence of gastroesophageal reflux at 1-year follow-up when a fundoplication was performed concomitantly with the diaphragmatic hernia repair [17]. A similar study confirmed the predictive value of having intrathoracic liver and patch closure at the time of diaphragmatic hernia repair for requiring a later fundoplication [18]. Some surgeons have therefore recommended performing a modified anterior fundoplication in high-risk patients at the time of CDH repair [19].

Children with type I spinal muscular atrophy may be good candidates for laparoscopic fundoplication. Early surgery increased the nutritional status of these patients and was associated with fewer

hospitalizations in the year following the procedure compared to the year before the operation [20]. Similarly, laparoscopic Nissen fundoplication at the time of gastrostomy tube placement was shown to improve survival in both type I and severe type II spinal muscular atrophy [21].

Age or weight should not preclude fundoplication in infants with significant gastroesophageal reflux symptoms or sequelae not responding to medical treatment. Laparoscopic Nissen fundoplication has been performed safely in small infants with low complication rates [22, 23]. Previous open surgery should also not be considered an automatic contraindication to laparoscopic fundoplication. In fact, several studies have shown excellent success rates and low conversion rates for laparoscopic fundoplication in children with previous open abdominal operations [24, 25]. Furthermore, fundoplication in general [26] and laparoscopic fundoplication in particular [27] were not found to increase the risk of shunt infection in children with ventriculoperitoneal shunts.

Laparoscopic fundoplication is feasible and beneficial to treat pathologic gastroesophageal reflux in children who underwent lung or heart-lung transplant with acceptable complication rates and outcomes [28]. Although fundoplication generally facilitates weight gain and nutritional status in children with severe congenital heart disease [29], children with hypoplastic left heart syndrome may have a higher morbidity and mortality during and after open fundoplication [30]. In these children, other nutritional options such as transpyloric feedings may have to be considered as an alternative until the patient has developed more stable physiology.

Most studies indicate that a fundoplication should not be added routinely to gastrostomy tube placement in neurologically impaired children [31, 32]. Postoperative morbidity was increased for patients having a routine fundoplication with their gastrostomy, and only 17 % of patients who underwent gastrostomy alone required a subsequent fundoplication at a later date for gastroesophageal reflux symptoms. Therefore, a more tailored approach is advised [33]. It is not clear what preoperative workup is necessary and which abnormal results should prompt a prophylactic fundoplication at the time of gastrostomy placement. Abnormal pH probe study alone was not a good marker to decide which neurologically impaired patients would benefit from a fundoplication at the time of gastrostomy placement [34]. In one study, clinical assessment had a 95 % positive predictive value in identifying patients who would require a gastrostomy [35].

Diagnostic Workup

Before considering a fundoplication, other entities that can mimic the symptoms of gastroesophageal reflux such as *H. pylori* infection, cyclic vomiting, rumination, gastroparesis, and eosinophilic esophagitis should be ruled out by careful medical evaluation.

A fluoroscopic contrast study of the upper gastrointestinal (GI) tract is usually the first step in the workup of gastroesophageal reflux disease. This examination allows the evaluation of the anatomy of the esophagus, the gastroesophageal junction, the stomach, the duodenum, and the ligament of Treitz. It allows the pediatric surgeon to rule out other anatomic reasons for reflux and vomiting, such as webs, stenosis, or malrotation. It also can detect hiatal hernia or peptic strictures of the lower esophagus which may modify the surgical plan or approach. In a study on 656 patients, significant findings other than gastroesophageal reflux or hiatal hernia were found in 4.5 % of upper GI studies performed in the workup for fundoplication [36]. Since it is merely a snapshot in time, and gastroesophageal is a dynamic disease that changes over the course of the day, the upper GI contrast study is not a sufficient examination to rule out or confirm gastroesophageal reflux. Its reported diagnostic sensitivity for gastroesophageal reflux is only about 31 % [36].

Reflux detected on pH probe in infants and children is extremely variable and depends on many factors such as age, feeding pattern, and positioning. It is therefore difficult to interpret the results. Boix-Ochoa proposed calculating the

relative time in which a pH below 4 is detected in the lower esophagus and counting reflux episodes lasting more than 5 min [37]. If a pH probe is ordered, it is important to standardize the circumstances as much as possible, discontinuing acid blockers for at least 3 days before the study and recording feeding and positioning as accurately as possible [38, 39].

A pH probe will not detect nonacid reflux due to gastric contents buffered by feeds or bile reflux. This drawback is circumvented by the more novel impedance study, in which the electrical resistance between multiple electrodes on an esophageal probe is measured. When gastroesophageal reflux is present, the electrodes are surrounded by liquid, conductivity increases, and consequently the electrical resistance drops. Therefore, the impedance study detects all types of reflux independent on the pH and has been found to be more sensitive for the overall detection of gastroesophageal reflux in children [40]. Despite these advantages, the interpretation of the results and their clinical significance faces similar challenges as discussed for pH probe above [41].

A pragmatic and low-cost method to assess for pathologic gastroesophageal reflux in children with either a nasogastric tube or a gastrostomy is performing a bolus feeding challenge under controlled condition during hospitalization. Goal bolus feeds are fed into the stomach, and clinical judgment is used to determine the presence of significant gastroesophageal reflux. If the patient vomits or shows other signs of intolerance such as posturing or coughing, a fundoplication may be indicated.

Some have argued that preoperative delayed gastric emptying does not adversely affect outcome of fundoplication, and therefore preoperative workup with a gastric emptying scan is not helpful [42].

Ultimately, the most important question in the workup of a child who may be a candidate for fundoplication is to predict the benefit the patient may have from the procedure. The current literature suggests that preoperative pH probe and even impedance study are poor predictors of surgical outcome after fundoplication [43, 44]. The workup for gastroesophageal reflux and the indication for fundoplication at this time remain a complex decision that should be individualized for each patient and should not be based on one sole study or clinical finding alone. With this in mind, it is not surprising that pediatric surgeons often decide on performing an anti-reflux procedure on nonobjective data such as parent preference, clinical impression, and recommendations by the pediatrician [45].

Techniques

Contrary to widely prevalent belief, the aim of a fundoplication procedure is not to simply create a tight lower esophageal sphincter. Rather, a well-performed fundoplication changes the geometry of the gastroesophageal junction based on the anatomic and physiologic anti-reflux mechanisms detailed in the introduction. It thereby creates a valve allowing the passage of food into the stomach, but preventing its reflux back into the esophagus.

Many different techniques using the same basic principles for this goal have been described (Fig. 93.2), including those by Nissen [46], Toupet [47], Thal [48], Colles [49], Boix-Ochoa [50], and Watson [51].

The type of fundoplication employed depends mainly on the experience and training of the particular surgeon. Some comparative studies have been performed. In a prospective randomized controlled study, laparoscopic Thal fundoplication had a higher recurrence rate (16 % versus 6 %), but a lower rate of severe postoperative dysphagia (2 % versus 12 %, respectively), compared to laparoscopic Nissen fundoplication [52]. Open Nissen fundoplication has been found to have higher long-term success rates than the open Boix-Ochoa technique, in which the fundus is placed anteriorly onto the esophagus and tacked to the margin of the right crus and diaphragm [53].

In the Nissen-Colles fundoplication, a stapler is used to vertically extend the esophagus into the stomach. It has been described for children and may be particularly useful in patients with previous esophageal atresia repair, in which the operation is limited by a short intra-abdominal segment of the esophagus [54, 55].

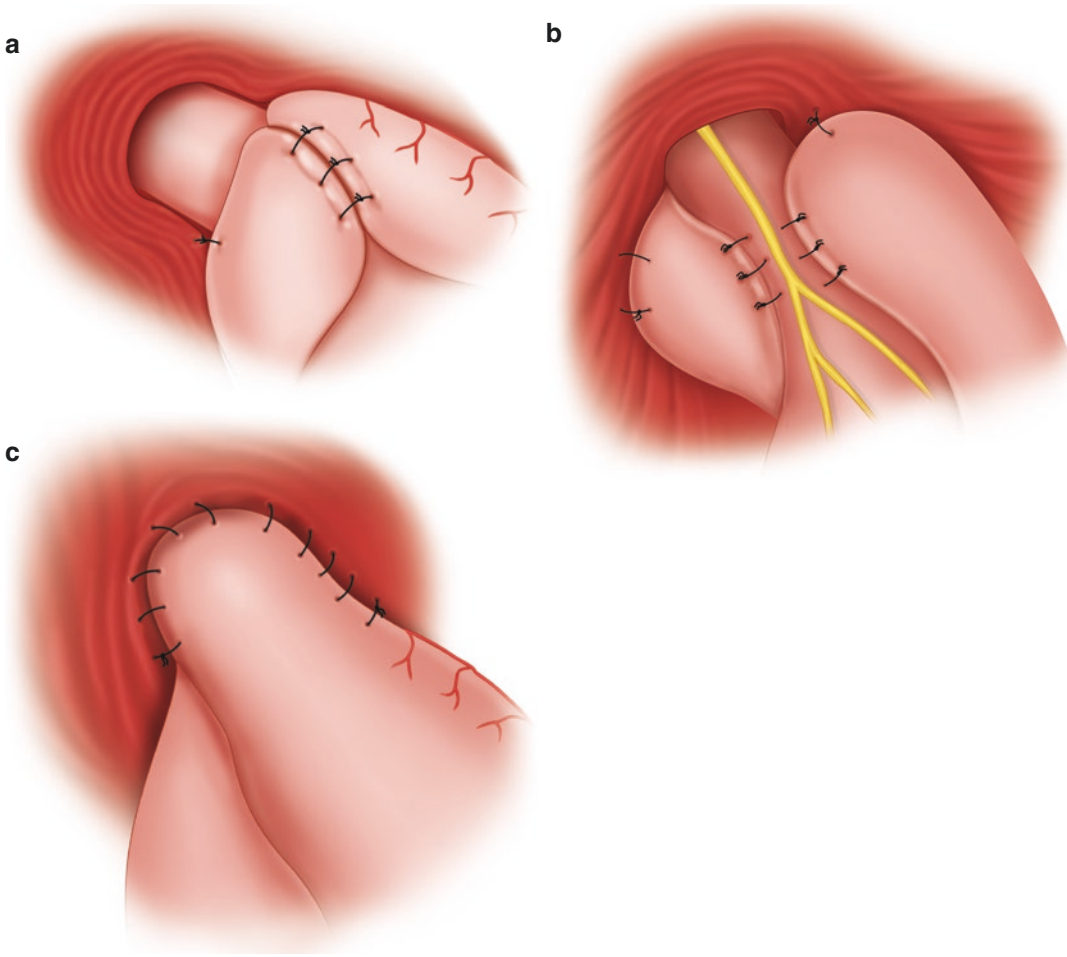

Fig. 93.2 The most commonly performed fundoplications in children are the Nissen fundoplication (**a**), in which a full 360° esophageal wrap is created and sutured around the lower esophagus. In the Toupet fundoplication (**b**), the fundus is pulled through a retroesophageal window and sutured to the anterolateral esophagus and the diaphragm, creating a 270° posterior cuff. The Thal (also called Dor) technique (**c**), consists of a 180° anterior fundoplication

Technically, a laparoscopic Nissen fundoplication is feasible in children without dividing the short gastric vessels (the so-called Rossetti modification) [56].

A complete fundoplication seems to be more effective in the treatment of gastroesophageal reflux, but partial fundoplication may have the advantage of less postoperative dysphagia [57]. This is still an ongoing debate. In a comparison of partial versus complete fundoplication, there were no differences in postoperative symptoms or complications, but more children achieved long-term medication-free recovery in the partial fundoplication group [58].

Regardless of technique, many surgeons place an esophageal bougie for calibration of the wrap before Nissen fundoplication. Recommended bougie size varies from 20F in patients around 2.5 kg to 40F for larger children around 15 kg. Wrap length generally varies between 1.5 and 3 cm [59].

Open Versus Laparoscopic

Since first described two decades ago, laparoscopic fundoplication has become the standard of care in many pediatric centers. In a large analysis

of 33,533 children, laparoscopic fundoplication was associated with less in-hospital mortality, shorter length of stay, and lower hospital charges, as well as decreased rates of decubitus ulcers and postoperative sepsis compared to open fundoplication [60]. Similarly, in a retrospective comparison of 50 laparoscopic versus 50 open fundoplication, the advantages of laparoscopic fundoplication included shorter length of stay, quicker feeding, and lower equipment, hospital room, and pharmacy charges. The main advantage of open fundoplication was shorter operating times and associated charges, while total charges were the same [61].

Recently, evidence has surfaced that minimal dissection of the esophagophrenic ligaments during laparoscopic fundoplication may decrease the rate of wrap migration into the chest [62]. This finding was confirmed by a subsequent prospective randomized controlled trial [63].

Gastric Emptying Procedures at the Time of Fundoplication

In the past, the question was posed whether a pyloroplasty or pyloromyotomy should be performed during fundoplication, either as a routine procedure or in cases where the preoperative workup shows delayed gastric emptying [64]. While some studies have shown improved gastric emptying with these types of procedures [65, 66], others have argued that preoperative delayed gastric emptying does not adversely affect outcome of fundoplication anyway [42] and that fundoplication promotes gastric emptying per se, making a synchronous gastric drainage procedure unnecessary [67].

Laparoscopic Nissen Fundoplication: Technical Description

The following is a description of the author's technique for laparoscopic Nissen fundoplication. The patient is positioned at the foot of the operating table. In small children, the legs are taped in a crossed configuration with padding. In older children, a modified lithotomy position in stirrups is preferred. A preoperative dose of prophylactic antibiotics is given, and an esophageal bougie of age-appropriate size [59] is placed. The first trocar is placed in the umbilicus and the capnoperitoneum is insufflated. Additional trocars are placed under laparoscopic vision in the midepigastrium, entering the abdomen just to the left of the falciform ligament, and in the left flank area anterior and inferior to the lower spleen tip. A liver retractor is introduced through a stab incision from the right upper quadrant and lifts up the left lobe of the liver, exposing the hiatus (Fig. 93.3a). The 30° camera can be changed to an additional trocar in the future gastrostomy site to give a more direct view onto the hiatus. The gastrohepatic ligament is then divided using the monopolar hook cautery up to the hiatus (Fig. 93.3b). The right esophagophrenic ligament is divided, and a retroesophageal space is dissected bluntly just posterior to the esophagus, respecting the posterior vagus nerve and leaving the hiatus as intact as possible without deliberate dissection toward the chest. The fundus of the stomach is then rotated medially anterior to the esophagus, exposing the gastrosplenic ligament and the short gastric vessels on the left (Fig. 93.3c). Only the most superior gastrosplenic attachments are taken down using the monopolar hook to expose the left esophagocrural ligament. The ligament is divided and at this time the retroesophageal space is completely patent. Only if the hiatus is open, one or two crural stitches are placed to approximate it posteriorly (Fig. 93.3d). All stitches are performed using 2-0 silk sutures and a ski-shaped needle. At this time, an instrument is passed through the retroesophageal space from right to left, and the esophagus is lifted gently anteriorly. Usually, the fundoplication is visible when the camera is oriented to look through the retroesophageal window from the patient's right side. The fundus is grasped, pulled through the space behind the esophagus, and the anteriorly remaining fundus is sutured to the transposed fundus using three silk sutures. A small portion of the lower esophageal muscle fibers is incorporated into the stitch (Fig. 93.3e). The suture line of the fundoplication should be

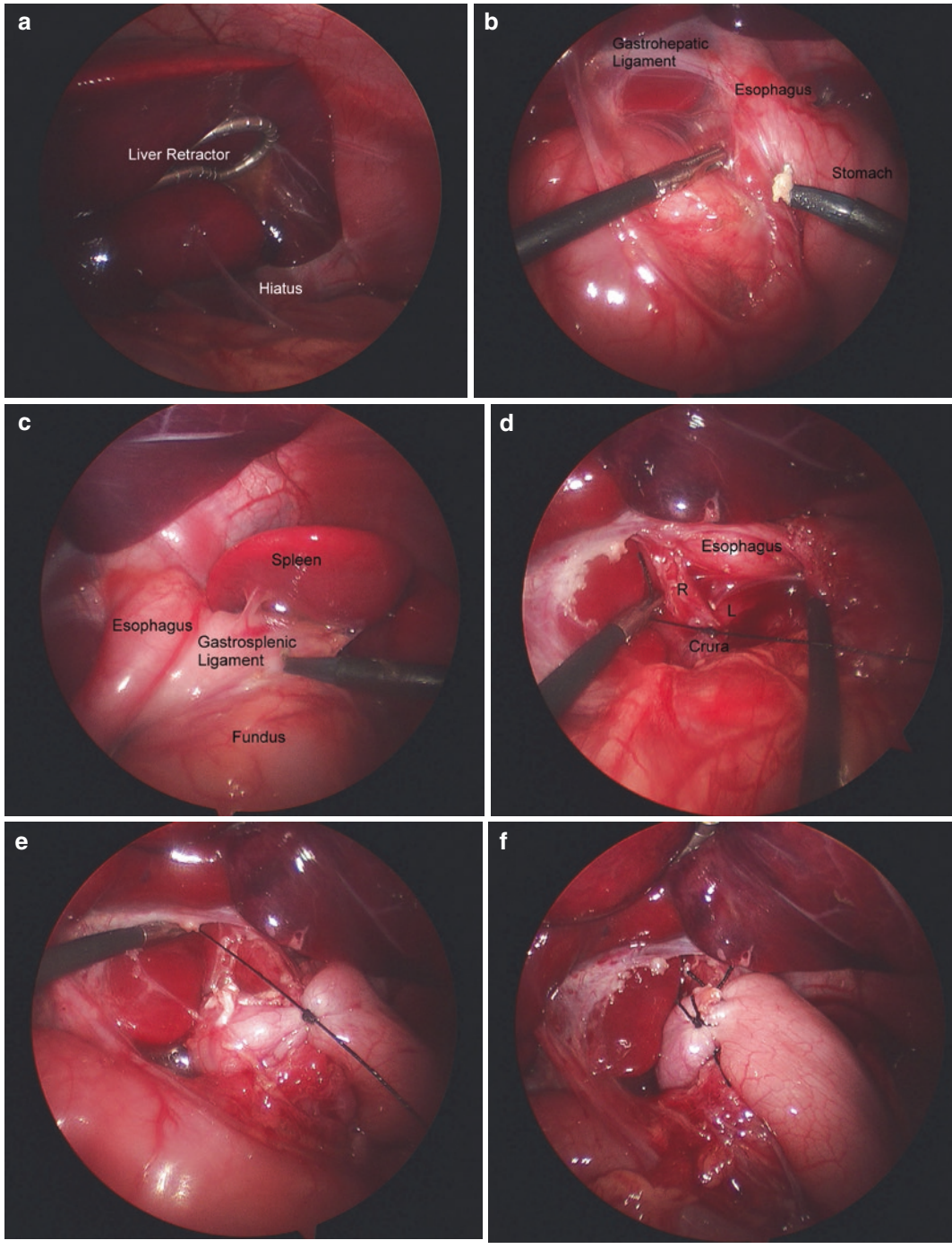

Fig. 93.3 Intraoperative images of laparoscopic Nissen fundoplication (see text for detailed explanation). The liver is retraced anteriorly, exposing the hiatus (**a**). The gastrohepatic ligament is opened to allow dissection of the space between the right crus and the esophagus (**b**). On the left, the superior part of the gastrosplenic ligament is divided as well (**c**). In this case, a crural stitch was placed posteriorly between the right (*R*) and left (*L*) crura (**d**). The posterior fundus is stitched to the anterior fundus around the lower esophagus (**e**). When completed, the suture line of the fundoplication is slightly medial and anterior (**f**)

located at the 10–11 o'clock position on the esophagus (anteromedially, Fig. 93.3f). Once completed, the bougie in the esophagus is withdrawn by anesthesia under vision. The capnoperitoneum is then desufflated and the endoscopic equipment is removed. Patients are allowed to have clear liquid diet when awake and advance to a no-chunk diet as tolerated. The no-chunk diet is maintained for approximately 3–4 weeks after the procedure, at which time regular diet is resumed.

Combination with Gastrostomy Tube

Laparoscopic gastrostomy tube placement can easily be performed along with laparoscopic fundoplication using the T-fastener or U-stitch technique [68]. Also, a percutaneous endoscopic gastrostomy (PEG) tube can be placed at the time of laparoscopic Nissen fundoplication with good results. Laparoscopic observation of the PEG placement may lower the procedure's complication rate [69].

Laparoscopic fundoplication in children who already have a gastrostomy tube in situ is feasible without increased complications [70]. Some surgeons prefer to take down the gastrostomy before fundoplication and perform a new gastrostomy thereafter, while others place the trocars around the gastrostomy site and leave it untouched. In this case, removing the gastrostomy tube before the sterile preparation and placing a sterile Foley catheter or similar into the gastrostomy site during the procedure are advisable.

Robotic and Innovative Approaches

Series of robotic-assisted fundoplication have been reported in children [71]. While it is more expensive, no clear benefits of the robotic approach have been shown in the clinical setting [72]. Operating times for the entire procedure were similar, although the dissection phase was about one third shorter with the robot. This temporal advantage was counteracted by a prolonged setup time for the robot [73]. The robotic approach has also been reported for redo Nissen fundoplication and fundoplication after gastrostomy tube placement in neurologically impaired children with acceptable perioperative complication rates and outcome [74]. One case-match control study comparing laparoscopic versus robotic versus open fundoplication including 50 pediatric patients in each treatment arm demonstrated longer operating times for robotic (160 ± 61 min) and laparoscopic (107 ± 31 min) compared to open fundoplication 73 ± 27 min, $P < 0.05$) with similar complication rates [75]. In an experimental study on infant pigs, conventional laparoscopic and robot-assisted fundoplication was equally effective, and there was a lower incidence of hemorrhage and pneumothorax in the robotic approach [76].

A single-incision laparoscopic approach for Nissen fundoplication has been described in ten children with complication rates and outcomes comparable to the conventional multi-trocar technique [77]. With the single-incision laparoscopic technique, all instruments and the laparoscope are brought in through a single incision in the umbilicus. When a synchronous gastrostomy is performed, the later gastrostomy incision is used as an additional access site, allowing for some ergonomic triangulation during the procedure. The most challenging part of the single-incision laparoscopic fundoplication is knot tying.

Inpatient admission and postoperative hospitalization for several days after a fundoplication are the current standard of care, although same-day outpatient laparoscopic Nissen fundoplication has been reported in a highly selected group of 19 children without any reported perioperative complications [78].

Recently, laparoscopic cardiaplication has been described as an alternative in patients with anatomic variants precluding formal fundoplication [79]. The technique entails a limited dissection along the most cranial greater curvature and subsequent imbrication of the cardia. It needs more formal evaluation before being universally recommendable.

The use of pledgeted mattress sutures rather than simple sutures for both the hiatal closure and the fundoplication reduced postoperative

recurrent reflux from 23.4 % to 5.7 % in a study of 384 children [80]. In another longitudinal study of a single surgeon using different methods to perform a Nissen fundoplication, additional sutures of the wrap to the diaphragm did not lessen the chance of failure, which was as high as 26 %, but reinforcing the actual fundoplication sutures with a second suture line eliminated wrap failure in 21 patients [81].

Radio-frequency application to induce circular collagen (scar) tissue in the area of the lower esophageal sphincter (Stretta procedure) has been reported in children, but has yielded only mediocre short-term outcome [82].

Results of Fundoplication

Fundoplication has made a tremendous difference in the lives of countless pediatric patients over the last half century. Studies show clear improvement in the children's symptoms and quality of life, particularly in those with neurological impairment [83, 84]. In a follow-up study of 40 patients who underwent a laparoscopic fundoplication, the parameters for growth, respiratory symptoms, proton pump inhibitor use, and global gastrointestinal quality-of-life index improved significantly after the operation. In this study the positive changes were similar in the 21 neurologically impaired and 19 healthy patients [85]. Furthermore, fundoplication leads to objectively measured improvement of gastroesophageal reflux measured by pH probe without adversely affecting esophageal motility [86].

The documented effects of fundoplication on respiratory symptoms are less striking. While 87 % of gastrointestinal reflux symptoms resolved in 151 children after Nissen fundoplication, only 45 % of patients with reactive airway disease had improvement in asthma symptoms or episodes of pneumonia postoperatively [87]. However, children with apparent life-threatening events (ALTEs) benefited from fundoplication, decreasing the readmission rate for ALTEs from 78 % before to 4 % after fundoplication in a cohort of 81 patients and follow-up times between 4 and 6 years [88].

Despite the unquestionable benefits of fundoplication, some pediatricians are concerned of inadvertent sequelae such as dysphagia, retching, dumping, and gas-bloat syndrome. In a systematic review of 15 studies of open and laparoscopic fundoplications, these complications were as high as 50 % in open procedures [89] and much higher than in the more recent laparoscopic studies. When counseling patients, it is important to take into account these advances. The reduction in morbidity due to the shift from open to laparoscopic technique may be one of the driving forces behind the increase in referrals for fundoplication in children over the last several decades [90].

The outcome of 385 open anti-reflux surgeries has been assessed by postoperative pH probe measurements, showing excellent efficacy and an immediate failure rate of just 2.9 % [91]. However, in a follow-up study on 176 children who underwent open fundoplication, dysphagia was recorded in 30 % and dumping syndrome in 3 % of the patients postoperatively [92]. Similarly, high rates of postoperative dumping (11.5 %), recurrent reflux (12.2 %), and dysphagia (12.8 %) were recorded in 148 patients who mostly underwent open fundoplication [93]. Of note, even with mortality rates as high as 13 % and major complications in 11 % of cases after open fundoplication in a cohort of 93 children, most parents were subjectively satisfied with the postoperative results on long-term follow-up [94].

In one of the first comparative retrospective studies on 120 patients, Collins et al. found a significantly shorter mean postoperative hospital stay (6.8 versus 10.7 days) and earlier time to full feeds (2.3 versus 4.8 days, respectively) for laparoscopic versus open fundoplication with similar complication rates [95]. The outcome of Nissen fundoplication in the laparoscopic era has dramatically improved. In a large analysis of 1,050 planned laparoscopic fundoplications in a single center, there were only two conversions to open technique. In this cohort, average operating times decreased from 109 min at the beginning of the observation period to 38 min in the last 30 procedures. The wrap failure rate was 4 %, and intraoperative complications occurred in only 0.26 % [96]. Another 5-year follow-up study of 238

neurologically normal children who underwent laparoscopic Nissen, Toupet, or Thal fundoplication demonstrated a 5 % intraoperative and 5.4 % postoperative complication rate. The incidence of dysphagia was 2.9 %, and only 2.5 % underwent a redo fundoplication during the observation period. At the 5-year follow-up mark, 96.3 % were free of reflux symptoms and without medications [97].

Although the postoperative cytokine response was found to be no different between open and laparoscopic fundoplication in a randomized trial of 40 children, postoperative immunosuppression measured by monocyte class II MHC was less pronounced in the laparoscopic group [98]. The same authors found no difference in postoperative analgesic requirement between open and laparoscopic Nissen fundoplication. However, fewer children retched, and there was a more pronounced decrease of insulin levels as an indicator of lower cortisol levels after laparoscopy [99].

In an analysis of 7,083 pediatric fundoplications across the United States between the years 2005 and 2008, 56 % were performed laparoscopically. Laparoscopic fundoplication was associated with much shorter length of stay (4 days versus 10 days) and lower cost (US$ 13,000 versus 22,000) when compared to open fundoplication. Furthermore, the laparoscopic group had a 21 % lower wound infection rate and a 51 % lower overall complication rate [100].

A recent systematic review of 17 prospective trials on fundoplication for gastroesophageal reflux disease including a total of 1,280 children found a median success rate of 86 % in providing complete relief of reflux symptoms without medication [57]. The surgical mortality rate was well below 1 %, and there were no cases of gas bloating reported in any of the included trials. Some studies reported less dysphagia with techniques that employ a partial wrap, with no other significant differences in outcome between techniques. Similar findings of shorter hospital stay, earlier feeding, and less morbidity with the laparoscopic approach were obtained in a meta-analysis of five studies [101]. Interestingly, robotic fundoplication was also associated with shorter postoperative stay compared to laparoscopic or open fundoplication in a study on 150 children [75].

Mortality after fundoplication does not usually result from the procedure, but rather from the comorbidities that prompted referral for the procedure in the first place. In a prospective observational study on 244 children who underwent Nissen fundoplication, 20 % died at a median follow-up time of 2.8 years [102]. The risk factors associated with mortality were cerebral palsy, female gender, and concomitant gastrostomy placement. Patients with cerebral palsy and gastrostomy placement had a particular high mortality rate of 41 % at 5 years follow-up, underlying the fact that many of these children have multiple morbidities contributing to the increased mortality.

Complications, Risks, and Alternatives

Despite the advances discussed above, fundoplication still has a relatively high failure rate (3–10 %) compared to other routine procedures in pediatric surgery in which the complication rates are usually around 1 %. Consequently, a detailed discussion about possible wrap dislocation, disruption, or migration and the potential need of a redo procedure is advisable with the patient and family before scheduling the operation. As discussed in the chapter on redo fundoplication, some patients may be predisposed to wrap failure, particularly those that exhibit preoperative retching with feeds.

Unfortunately, there is no reliable method to avoid postoperative retching. Some surgeons advise decreasing the feeding rate or venting the gastrostomy between feeds and when retching occurs. According to one study, a pureed gastrostomy tube diet in lieu of the more conventional formula feeds may reduce the incidence of postoperative gagging and retching after fundoplication by modulating stomach emptying [103].

At times, the intraoperative findings preclude the completion of a planned fundoplication. Severe adhesions may increase the risk of the hiatal dissection, or the stomach may not be large enough to perform the desired loss wrap. In these cases, a Roux-en-Y feeding jejunostomy may be

an alternative [103], although the complication rate was found to be as high as 51% [104]. Placing a gastrostomy for later gastrojejunostomy tube placement is another option [105]. In an observational study, this approach had similar outcome to fundoplication in terms of survival or postoperative pneumonias [106].

Conclusions

Fundoplication has conferred immense benefits to countless children suffering from gastroesophageal reflux disease. When performed laparoscopically and using contemporary technique, outcome is usually excellent, and the morbidity and mortality from the procedure are low.

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Reoperative MIS Fundoplication

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Oliver J. Muensterer, Carroll M. Harmon, and Keith E. Georgeson

Introduction

Nissen fundoplication has become the procedure of choice in children with gastroesophageal reflux disease (GERD) refractory to medical therapy [1]. Most procedures are performed laparoscopically, with a low perioperative complication rate and minimal morbidity. Unfortunately, these excellent short-term results are dampened by a relatively high long-term failure rate of 2.5–25 % [2–4]. At our own institution, the long-term failure rate over the last decade is around 12 %. The most common underlying mechanisms for fundoplication failure include hiatal herniation into the chest, as well as slippage, misplacement, or breakdown of the wrap [5]. This can lead to recurrent gastroesophageal reflux and the sudden onset of recurrent symptoms. This chapter describes the risk factors and mechanisms of fundoplication failure, the indications for redo fundoplication, and the surgical technique.

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Risk Factors for Failure

Pediatric surgeons must be well aware of the risk factors for fundoplication failure before performing the procedure in a child. This awareness impacts on surgical indications, the discussion with the caregivers about the procedure, and selection of the technique most appropriate for the individual patient. General risk factors for fundoplication failure are neurologic impairment, younger age, lower body weight, and surgery performed via the open rather than the laparoscopic approach, while the presence of a gastrostomy and older age seems to have a protective effect in multiple regression analysis [6].

Specifically, a matched case-control study of over 400 pediatric patients under 6 years of age showed that the presence of a hiatal hernia or dysphagia associated with an esophageal stricture were preoperative risk factors for recurrent GERD after a fundoplication [7]. In the same study, 7.2 % of 417 laparoscopic fundoplications performed at this particular center were redo procedures, of which 80 % presented with recurrent reflux symptoms and 20 % with dysphagia and a tight wrap. One-third of the patients who underwent a redo procedure were neurologically impaired. Furthermore, previous esophageal atresia repair was identified as a potential preoperative risk factor for fundoplication failure in up to one-third of these patients [8].

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Neurologic impairment is well documented as one of the prime factors associated with recurrent reflux after fundoplication. In a retrospective analysis of 127 children, gastroesophageal reflux eventually recurred after laparoscopic Nissen-Rossetti fundoplication in 12 % of neurologically impaired children, but in only 2 % of their neurologically normal peers [9]. However, the recurrence rate in neurologically impaired children has been recorded as low as 6 % elsewhere [10]. In another report, 19 of 252 open pediatric Nissen fundoplications underwent reoperation, with an average interval between the procedures of 1.6 years (range 1 month to 5.5 years), and 11 of the 19 children being neurologically impaired [11]. Neurologic impairment was also found to be an independent risk factor for postoperative complications in 12 out of 106 kids who underwent laparoscopic Nissen fundoplication [12].

The main mechanism of failure in this cohort was herniation of the fundoplication through the hiatus in eight, and incompetence or dehiscence of the wrap in six cases. At our own institution, lower age, the presence of retching, and performing postoperative esophageal dilatations were identified as postoperative risk factors [13]. Although retching has also been associated with fundoplication failure in older studies [14], a causal nature has not been confirmed so far [6].

Intraoperative technique may predispose to fundoplication failure in children. In a recent randomized controlled multicenter study on 177 children who underwent fundoplication, performing an extensive versus minimal dissection of the hiatus increased the risk of recurrent GERD from 7.8 % to 30 % and the need for redo fundoplication from 3.3 % to 18.4 % [15]. The current standard should therefore be to leave the esophagocrural and esophagophrenic attachments intact during the dissection phase of the procedure.

Hiatal hernia was the most common cause of fundoplication failure in 30 of 66 (46 %) retrospectively reviewed children requiring redo fundoplication, followed by a combination of herniation and disrupted fundoplication in 22 (3 %), disruption of the wrap alone in 10 (15 %), and too tight a wrap in 4 (6 %) patients [14]. There is some evidence that the mechanisms of failure may be different for laparoscopic versus open fundoplication. While most laparoscopic failures were found to be due to herniation and fundoplication dehiscence, wrap slippage was the primary reason for failure in the open group [16].

Indications for Redo Fundoplication

Redo fundoplication is indicated when symptoms of gastroesophageal reflux recur after a fundoplication, and cannot be managed by conservative means such thickened feeds, positioning, proton-pump inhibitors, or prokinetics. In some cases, when the wrap is partially intact, the antireflux effect of the wrap may not be completely annihilated, and the addition of medication may avoid the need for redo surgery. If conservative methods are unsuccessful, or if a hiatal hernia is present, redo fundoplication should be performed.

In many cases, the caregivers can describe a discrete time point at which the patient started vomiting again or experienced a significant deterioration of clinical status. Anatomically, up to 75 % of fundoplication failures are associated with a hiatal hernia, and in 49 %, the wrap is intact [17]. As mentioned above, the wrap may have become too lose, and occasionally, the wrap can slip to a location below the esophagogastric junction, rendering it ineffective.

The diagnostic procedure of choice in patients with recurrent reflux symptoms is a radiographic upper gastrointestinal contrast study, either via the oral route or, if present, through a gastrostomy tube if the patient cannot tolerate liquids by mouth (e.g., in cases of aspiration). The study is performed to evaluate the fundoplication, which, if intact, is usually visible as an indentation at the level of the gastroesophageal junction, and to rule out an associated hiatal hernia. In some cases, frank gastroesophageal reflux is evident, although the contrast study can only document a snapshot over a discrete, limited time period. In clinically ambiguous cases, esophageal 24 h pH-probe

recording, manometry, or impedance measurements are indicated to confirm recurrent reflux. Esophagoscopy can also be helpful, either by identifying an anatomic abnormality such as hiatal hernia, frank esophagitis, or the presence of lipid-laden alveolar macrophages in bronchoalveolar lavage [18].

Treatment and Technique

Over the last decade, fundoplication by laparoscopy has been established as the standard and preferred technique in children. However, many pediatric surgeons still revert to an open procedure to treat recurrence. There is no doubt that redo fundoplication is technically much more challenging than the primary operation, illustrated by the relatively long mean operating time of 140 min for the redo procedure, with a range of 110–240 min [7]. Several studies have looked at the technical aspects and practicability of laparoscopic versus open redo fundoplication.

In one report, laparoscopic reoperation was feasible in 10 out of 15 cases, and the redo operation was more likely to be completed laparoscopically after a previous laparoscopic than after an open initial fundoplication (7 of 8 versus 3 of 7 cases, respectively). Also, it was easier to perform after a previous Thal or Toupet fundoplication compared to an initial Nissen fundoplication [19]. In a smaller study, one out of four attempted laparoscopic redo fundoplications was converted to the open procedure [20].

During laparoscopic redo fundoplication, care must be taken while placing the first trocar. Due to the previous operation, bowel loops may be adherent and need to be identified. We always perform a blunt, open access technique, but would recommend it especially for all laparoscopic redo operations.

In most cases, dense adhesions are found between the esophagus, the stomach, the diaphragm, and the liver (Fig. 94.1a). Sharp dissection of these adhesions using the Metzenbaum scissors under traction and countertraction is usually most effective. The operation itself can be quite bloody, and we generally attach unipolar electrocautery to the scissors in the laparoscopic procedure, so that small bleeding vessels can be cauterized immediately during the dissection without changing instruments. Occasionally, newer tissue sealing instruments can be helpful, although collateral heat dissipation to the stomach or esophagus is a concern which makes sharp dissection with the cold scissors the safer option. Because of the potential for bleeding, a suction-irrigation system should be set up and available during the procedure. It is advisable to have blood available intraoperatively in case significant hemorrhage is encountered.

Because fundoplication failure may be due to many factors, a tailored approach is required. In some cases, hiatal hernia repair may be required only, while in others, the actual wrap must be revised as well [21].

In principle, the hiatus of the diaphragm must be dissected (Fig. 94.1b) and a potential hiatal hernia reduced. The hiatus is subsequently closed securely anteriorly and posteriorly around the esophagus with a dilator in place using permanent braided sutures (we prefer 2-0 silk on a ski-type needle, Fig. 94.1c, d). If the wrap has unraveled, it should be completely taken down, and a new, geometrically sound and secure wrap is created (Fig. 94.1e, f). In cases where the wrap is loose or stretched, simple reinforcement and tightening with additional sutures can be attempted. Laparoscopic redo fundoplication has been performed in the Nissen, Nissen-Rossetti, and Toupet technique [7].

Some surgeons have proposed using a patch to reinforce the hiatal closure in redo fundoplication. In adults, a posteriorly placed polypropylene mesh has been used for this purpose in both laparoscopic Nissen and Toupet fundoplications [22]. Using this approach, only 2 of 66 patients developed a recurrent hiatal hernia over a follow-up time of 5 years. In children, one study described no recurrences in eight redo Nissen fundoplication cases repaired with a Surgisis mesh compared to 31 % of 13 patients repaired without mesh in a mean follow-up time of 26 months [23]. While reinforcing the hiatus with

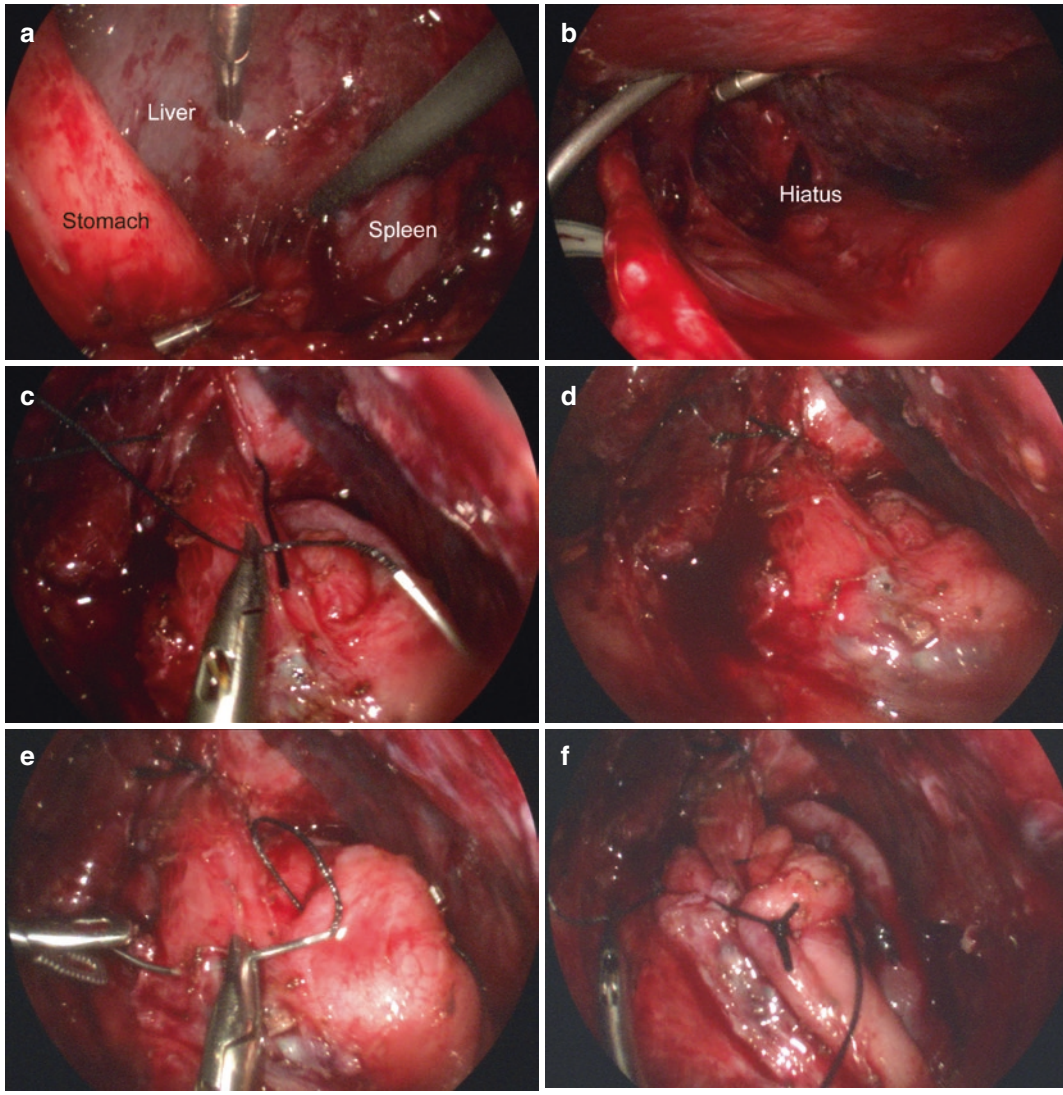

Fig. 94.1 Every redo fundoplication requires a tailored approach. In most cases, dense adhesions must be taken down carefully (**a**) to expose the hiatus and the anatomical problem, in this case an unraveled wrap and a widely open esophageal hiatus (**b**). With the largest possible size dilator in the esophagus, the hiatus is closed anteriorly (**c**). Subsequently, the unraveled wrap is exposed (**d**) and recreated (**e**, **f**)

a mesh may decrease the recurrence rate, the scarring and adhesions induced by the patch make any future operation more challenging in our experience.

An alternative to redo fundoplication may be lower esophageal sphincter radiofrequency ablation [24]. Of six patients treated in this fashion, five were asymptomatic 3 months after the procedure, and half discontinued antacid medications. One patient went on to undergo a redo fundoplication, and in another patient, the radiofrequency ablation was repeated 10 months later.

Another option described for children with neurological impairment who are exclusively tube fed is the esophagogastric separation. However, this procedure carries a high complication rate, with half of patients not tolerating their saliva, and reoperations for either a colonic perforation or

paraesophageal hernia in two of ten patients [25]. It should therefore be reserved for particularly severe and otherwise unmanageable cases.

Results of Redo Fundoplication

Early Results

As mentioned before, fundoplication, in general, and redo fundoplication, in particular, are some of the most complication-prone operations in pediatric surgery. In adults, the success rate of laparoscopic redo fundoplication was only 86 % [26], similar to the 17 of 19 (89 %) children reported to be free of symptoms after open redo fundoplication in a recent study [11]. In another report, redo fundoplication failed to resolve symptoms in 20 % of 66 children with recurrent reflux, and 5 of those eventually were treated by a second redo fundoplication [14].

Laparoscopic redo fundoplication was found to be more challenging in adults, and resulted in a hospital stay that was three times longer than after primary fundoplication (3 days versus 1 day), as well as significantly higher costs [27].

In one study, redo fundoplication was successfully completed laparoscopically in 89 % of first operations and 68 % of redo operations, highlighting the increasing degree of difficulty and intraoperative conversion rate. Consequently, the average operating times of redo fundoplication were over 2 h [17]. On the other hand, all 118 laparoscopic redo Nissen fundoplications were completed without conversion in a single-surgeon case series, with an average operating time of 100 min, and a failure rate of only 6 % [28].

Long-Term Results

In general, the risk of recurrent gastroesophageal reflux increases with every redo fundoplication performed in a patient. Roughly one-quarter of patient required another redo procedure after the first one [17]. Neurologic impairment again is a significant risk factor, with new reflux symptoms appearing in 6 out of 30 patients (20 %) after a follow-up period of 2–12 years, 5 of which were neurologically impaired [7]. Half of neurologically impaired children with recurrent reflux symptoms after a fundoplication eventually failed conservative treatment and eventually underwent a redo fundoplication [12].

Table 94.1 Results of redo fundoplication at the Children's Hospital of Alabama [11]

	1st redo ($n=72$)	2nd redo ($n=19$)	3rd redo ($n=3$)
Conversion to open surgery	8 (11 %)	6 (32 %)	1 (33 %)
Operation time (min)	132 ± 60	156 ± 54	204 ± 18
Length of stay (days)	5.0 ± 4.8	4.9 ± 3.2	6.0 ± 3.0

In a cohort study of 221 adults, redo fundoplication was less effective in suppressing reflux symptoms than the primary operation. Average quality of life scores were lower as well after a redo procedure, compared to the first fundoplication, particularly on long-term follow-up more than 2 years after surgery [29].

At the Children's Hospital of Alabama [17], conversion rates were higher, and operative times were longer with each redo procedure attempted laparoscopically on a patient (Table 94.1).

Complications and Risks

Apart from the risk of recurrent reflux highlighted in the previous section, other perioperative complications have been described. In a recent publication, one pleural perforation occurred in 30 redo fundoplications [7]. Intraoperatively, pleural perforation may lead to pneumothorax, and sudden respiratory deterioration of the patient. Whenever the ventilatory status of the patient acutely changes, one must think of this possibility. A chest radiograph and tube thoracostomy may be indicated.

In at least one instant, a Dacron patch placed around a large hiatal defect eroded into the esophagus and required reoperation [21]. For this reason, we prefer to use bioabsorbable patches made from porcine or bovine collagen.

As discussed previously, intraoperative complications can also include significant bleeding when taking down extensive adhesions. An increased risk of esophageal or gastric perforation has also been described [11].

When discussing the complications of a redo fundoplication, one must weigh them carefully against the risks of not performing the operation. Children without protective airway reflexes may aspirate refluxed gastric contents into their lungs, leading to pneumonia or even asphyxia. In a long-term follow-up study [30], 80 % of 20 patients who underwent an open redo fundoplication did well after the procedure. One of the remaining four patients who again presented with recurrent reflux symptoms underwent a third Nissen fundoplication and also did well. The others were managed conservatively, and one of these eventually died.

Conclusion

Fundoplication is a procedure with a high recurrence rate. A pediatric surgeon who performs fundoplications should be familiar with the signs and symptoms of recurrent gastroesophageal reflux, knowledgeable on the diagnostic work-up of children with suspected wrap failure, and skilled in performing a redo fundoplication if indicated. The laparoscopic approach may be superior to open methods, even for these more difficult redo cases. Depending on the mechanism of recurrent reflux, the fundoplication wrap may require tightening or complete reconstruction, and a hiatal hernia should be repaired. The risk of recurrent reflux in a patient increases with the number of redo fundoplications performed.

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Endoscopic Approaches to the Treatment of GERD

95

Mike Thomson

Gastroesophageal reflux disease (GERD) is symptomatic reflux associated with sequelae. These include failing to thrive, refractory wheezing coughing aspiration, acute life-threatening events, apnea, chronic otitis media, sinusitis, hematemesis, anemia, esophageal strictures, and Barrett's esophagus [1, 2]. A follow-up of 126 children with gastroesophageal reflux disease in infancy showed 55% were symptom-free by 10 months and 81% by 18 months of age [3]. However, those with frequent symptoms (>90 days) in the first 2 years of life are more likely to have symptoms by 9 years of age [4].

Gastroesophageal reflux treatment aims to achieve symptom relief while preventing complications. Patients who fail to achieve control with medical therapy may have persistent severe esophagitis or become long-term dependent on antireflux treatments. In such cases an antireflux procedure may be indicated [1, 5]. The principle of surgery in gastroesophageal reflux disease is to form some kind of reconstruction of the antireflux barrier, although exactly how efficacy is achieved is not fully understood. Open Nissen's fundoplication has been the treatment of choice to date, but is invasive and associated with morbidity and mortality [6, 7]. In recent years laparoscopic fundoplication has become popular and, in general, has replaced the open Nissen's procedure, although superior efficacy and safety has yet to be demonstrated [8]. With the laparoscopic procedure, cosmesis is clearly superior, and in adult studies, complications appear less common, with good success rates [9, 10]. It could be argued therefore that there remains little or no place for open antireflux procedures in pediatrics.

Three endoscopic techniques have been devised and used for treatment of pediatric GERD. These are described below.

Endoscopic Suturing Devices

Endoluminal gastroplication makes use of an EndoCinch® sewing machine attached to the endoscope (gastroscope) placing three pairs of stitches below the gastroesophageal junction to create three internal plications of the stomach [1–16]. Plications may be applied in any manner dependent on operator preference. These may be applied circumferentially or longitudinally. The authors have a preference of placing two plications circumferentially 1.5 cm below the gastroesophageal junction and one 0.5 cm below the gastroesophageal junction, which we believe anatomically may be superior to other formations [11, 12] (Figs. 95.1, 95.2, 95.3, and 95.4).

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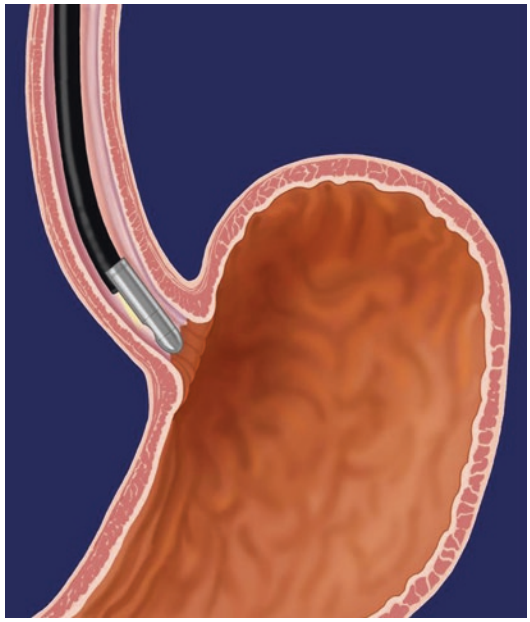


Fig. 95.1 EndoCinch front-mounted on endoscope

Endoluminal gastroplication is now routinely carried out as a day-case procedure in adults. Preliminary studies have shown it to be quick, noninvasive, effective, and safe [11, 17]. Results are comparable to the laparoscopic fundoplication in adults [8, 10, 11, 17], which has been studied as a preferable alternative choice to an open Nissen's fundoplication [11, 18].

Recently, the authors have reported use of EndoCinch® (endoscopic gastroplication using a flexible endoscopic sewing device) in the treatment of 17 children (8 males, median age 12.9 years, range 6.1–17.7; median weight 45 kg, range 16.5–75) with gastroesophageal reflux disease refractory to, or dependent on (>12 months) proton pump inhibitors [19]. All patients showed posttreatment improvement in symptom severity, frequency, and validated reflux-related quality of life scores ($p<0.0001$) (Fig. 95.5). At 36 months median follow-up, 11/17 patients were asymptomatic and off all antireflux medica-

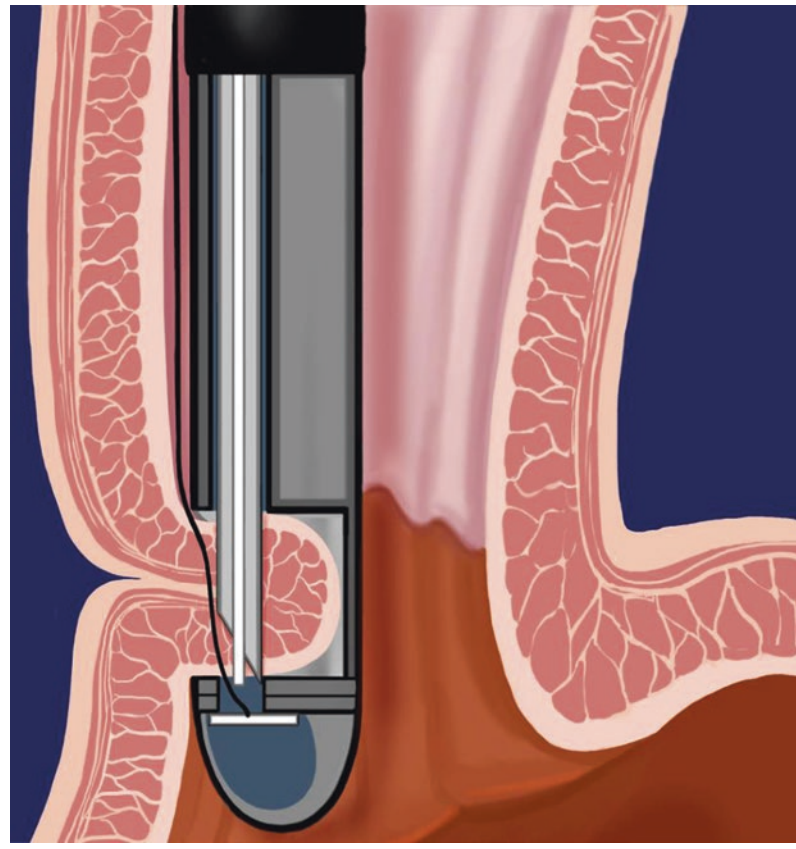


Fig. 95.2 Suction applied and full-thickness tissue capture followed by needle and pusher wire placement of stitch

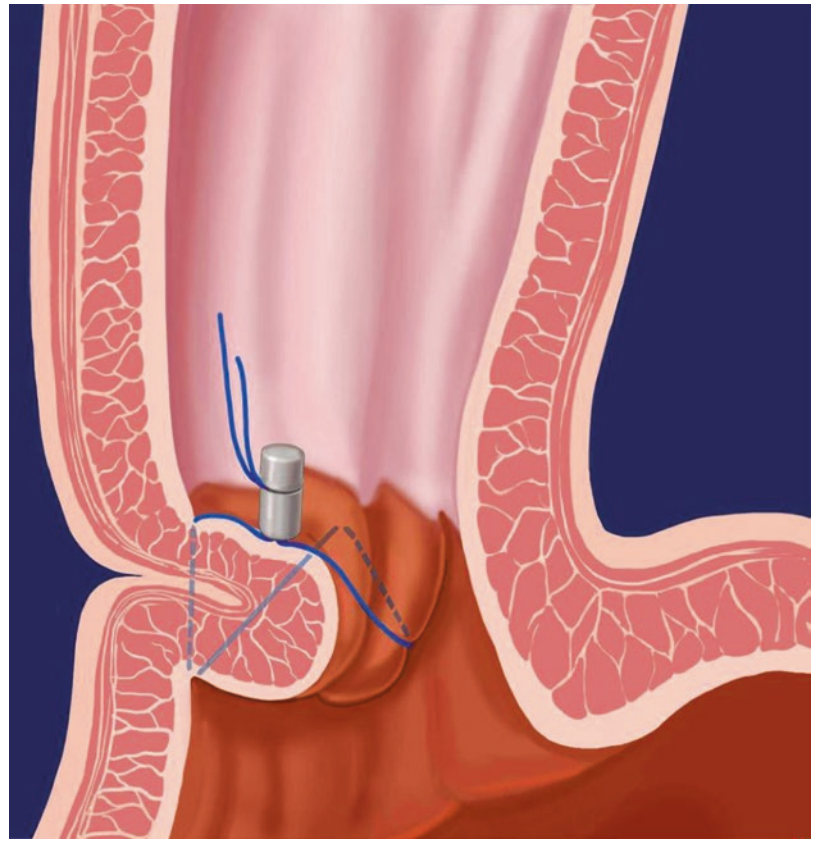


Fig. 95.3 Endoscopic gastroplication. This figure the pattern of a zigzag stitch when applied with an EndoCinch® sewing machine

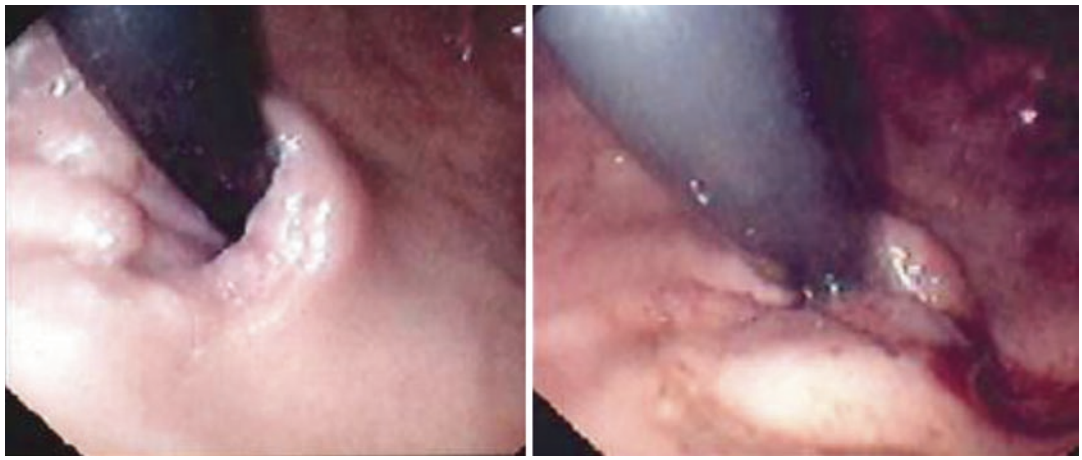


Fig. 95.4 View (J maneuver) of a lax GE junction in a child with major reflux after application of stitch with the EndoCinch®

tions. At 12 months follow-up, all pH parameters improved and had returned to normal in eight out of nine who underwent pH studies (reflux index fell from 16.6 % (0.9–67 %) to 2.5 % (0.7–15.7 %) ($p < 0.0001$)) (Fig. 95.5).

The duration of action is open to ongoing assessment and debate and has not been particularly impressive in adult studies. The reasons for superior efficacy and duration in children may be conjectured and may be due to some or

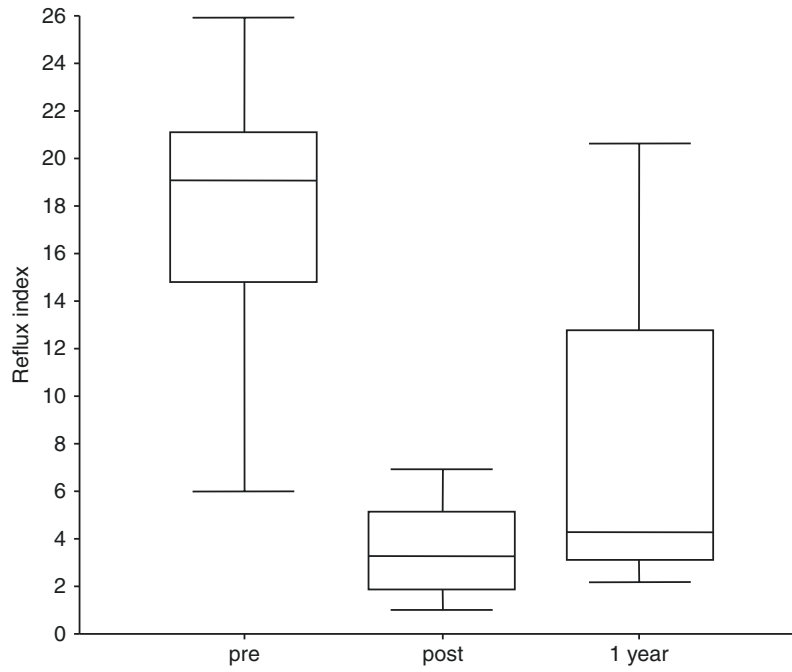


Fig. 95.5 EndoCinch® pediatric series pH efficacy at 1 year

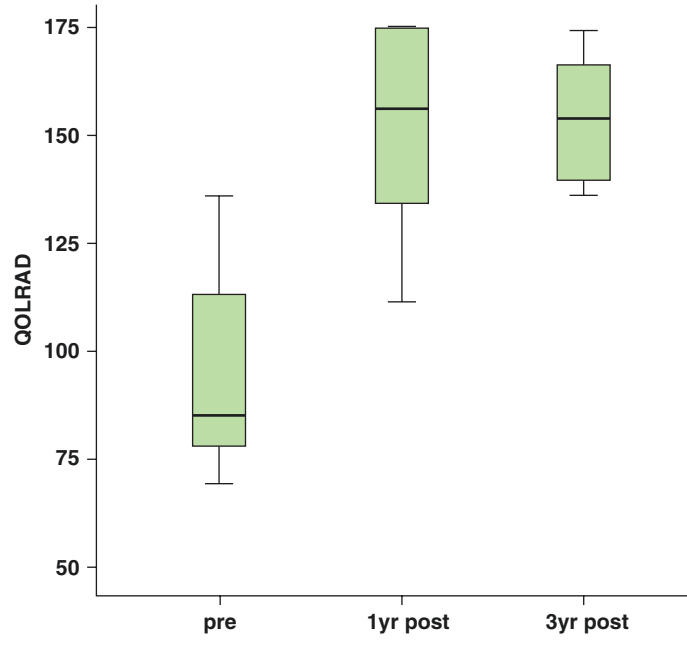
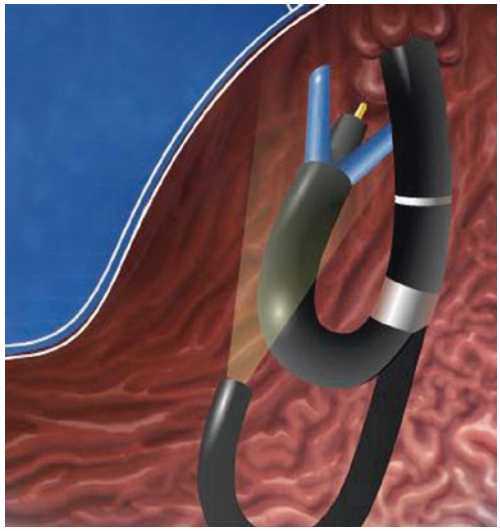


Fig. 95.6 Significant improvement in the total QOLRAD score 1 and 3 years after gastroplication with the EndoCinch®

all of the following: three pairs vs two pairs of sutures, greater time and care taken by the operator allowed by general anesthetic with the added advantage of the absence of movement or retching during the procedure, and lastly the relatively deeper suture depth in the thinner pediatric esophagus compared to the larger adult one. Data are now available indicating medium term success in terms of reflux-related quality of life scoring at 3 years post-EndoCinch and in terms of avoidance of PPI need in the majority of patients [20]. This is a small study but worthy of mention (Fig. 95.6).



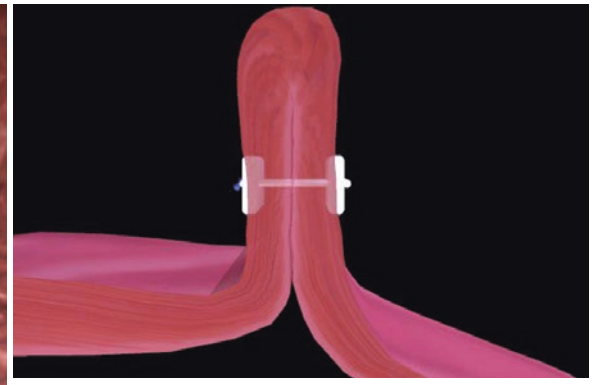


Fig. 95.7 and 95.8 Application of the Full-Thickness Plicator® (NDO Surgical)

Despite the loss of sutures on observational follow-up studies, some efficacy has been maintained, and the human and porcine endo-ultrasound studies of Liu et al., along with cadaveric analysis of the porcine model post-EndoCinch®, may throw some light on this observation [21]. They suggest that the tissue remodeling in response to the foreign body, which is the suture, resulting in significant hypertrophy of the circular muscle layer of the esophagus may be the reason.

Nevertheless, EndoCinch® has not maintained its initial enthusiastic uptake and has been recently superceded by the next generation of full-thickness gastroplication trans-oral endoscopic techniques.

The next to appear was the Full-Thickness Plicator® (NDO Surgical). This is placed under direct vision with a neonatal size endoscope passed through a specially designed endoscopic delivery system with an outer diameter of more than 20 mm. The retroflexion of both allows observation of firstly the opening of the jaws of the device, followed by the insertion of the corkscrew into the fundal tissue allowing capture of the fundus and withdrawal into the jaws which are then closed. A pre-tied full-thickness plication is then applied by the mechanism of shutting the jaws, and a serosa to serosa plication is made (Figs. 95.7, 95.8, and 95.9). A multicenter adult study has shown acceptable efficacy and a reduction of PPI requirement in a small adult cohort [22], and further study is necessary before this should be applied to children – the device is size- and age-constrained due to its large outer diameter.

EsophyX

This device is representative of an alternative to the Plicator technology along a similar theme, although not identical.

The novel Trans-oral Incisionless Fundoplication (TIF)® procedure using EsophyX® mimics antireflux surgery in constructing an anterior partial fundoplication with tailored delivery of multiple fasteners during a single-device insertion (Figs. 95.10 and 95.11) [23]. The TIF procedure was designed to restore the antireflux competency of the gastroesophageal junction through reducing small hiatal hernias, increasing lower esophageal sphincter (LES) resting pressure, narrowing the cardia, and recreation of the acute angle of His [24–28].

Clinical results with TIF at 1, 2, and 3 years support its efficacy in eliminating heartburn and regurgitation, reducing the daily use of PPIs, nor-

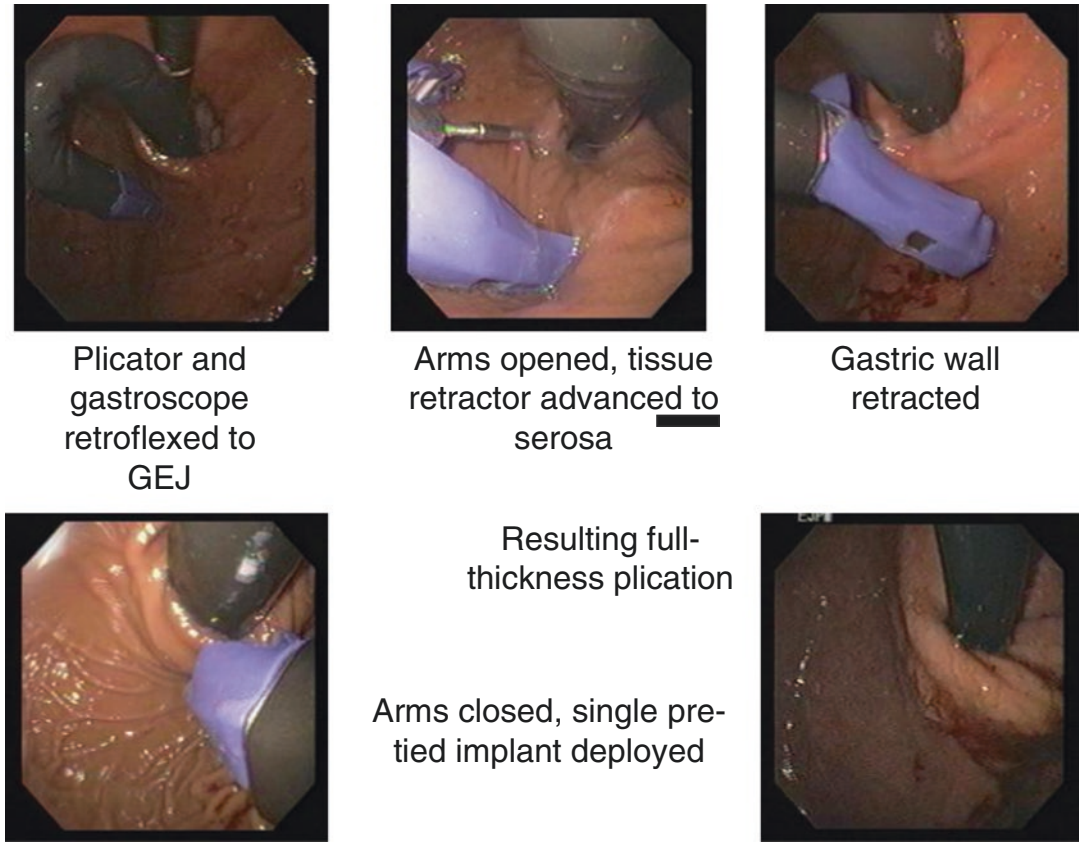


Fig. 95.9 Retroverted views of stages of application of Full-Thickness Plicator® (NDO Surgical)

malizing esophageal acid exposure, and reducing proximal extent of refluxate [24, 27, 29–31]. Based on a 1-year result, FDA cleared EsophyX in September 2007 for the treatment of GERD and small (<2 cm) hiatal hernia [24].

The TIF procedure has been demonstrated to be safe in adults. Post-TIF adverse events are mild and transient and include musculoskeletal and epigastric pain, nausea, and dysphagia up to 1 week secondary to sore throat [24, 29]. Only three esophageal perforations have been reported to date for 3,000 cases performed worldwide. None of the subjects experienced chronic dysphagia, gas bloating, and diarrhea at long-term follow-up [24].

A feasibility study was started in December 2008 after obtaining appropriate training in the use of the EsophyX® device in its second iteration – the so-called TIF2 procedure. The feasibility study was conducted with 12 children (8 male) with a median age of 12.25 years (8–18 years) and weight of 38.2 kg (26–91) [32]. The median duration of GERD symptoms was 45 months (24–70), and all subjects were on GERD medication for more than 6 months. The median pre-TIF2 reflux index of treatment was 11.4 % (6–48). Hiatus hernia was present in 17 % (2/12). Median operative time was 42 min (range 25–94). Adverse events were experienced by three subjects and consisted of mild or moderate pharyngeal irritation and epigastric pain. Two of the three subjects also had retrosternal chest pain and were subsequently found to have pneumomediastinum on CT chest but no leak on barium swallow. One of these two patients had pyrexia accompanying chest pain and was treated for possible mediastinitis and discharged home after 5 days of intravenous antibiotics. Subsequently, CO_2 insufflation was employed, and more rapid absorption resulted in no further periprocedural mediastinal gas leak.

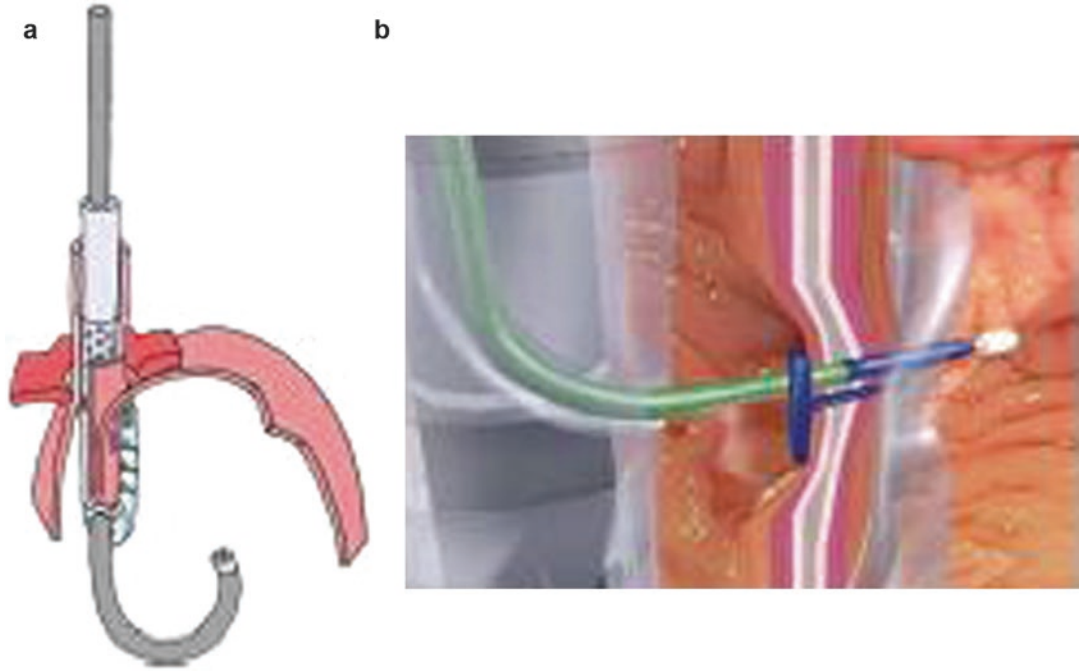


Fig. 95.10 Distal end of the EsophyX® device (**a**) and SerosaFuse Fastener (**b**). The valve is constructed by drawing tissue into the device with the aid of a helical retractor. The tissue mold is then closed over the retracted tissue and the fasteners are deployed. The fastener is delivered by a pusher that slides over a stylet (Illustration from Jobe et al. [25])

At 6-month follow-up, all subjects ($n=10$) discontinued PPIs; 80 % were asymptomatic and 70 % had normalized or clinically significantly reduced reflux index (10 % time pH <4). The results of this feasibility study showed that the TIF procedure was feasible, safe (with CO_2 insufflation), and clinically effective in treating GERD in children. Ongoing studies are occurring.

Delivery of Radiofrequency Energy (the Stretta® System)

The Stretta® system has two parts, one a Stretta® catheter and the other Stretta® control module. The Stretta® catheter is a flexible, handheld, single-patient use device that delivers radiofrequency energy generated by the control module (Fig. 95.12). It is inserted into the patient's mouth and advanced to the gastroesophageal junction. A balloon is inflated and needle electrodes are deployed into the tissue. Radiofrequency energy is delivered through the electrodes to create thermal lesions in the muscle of the lower esophageal sphincter and gastric cardia. As these lesions heal, the tissue contracts, resulting in a reduction of reflux episodes with improvement in symptoms. The Stretta® control module delivers this radiofrequency, while at the same time providing feedback to the physician regarding treatment temperatures, tissue impedance values, elapsed time, catheter position measurement, and irrigation rate.

This treatment has been used in adults since 1999. Complications are rare, but among reported are ulcerative esophagitis with gastroparesis, esophageal perforation, and a case of aspiration following the procedure [32–34]. Short-term (1 year) success was reported in an open-label trial. In a prospective study (nonrandomized controlled trial) of 75 patients (age 49 ± 14 years, 44 % male, 56 % female) undergoing laparoscopic fundoplication and 65 (age 46 ± 12 years, 42 %, 58 % female) undergoing

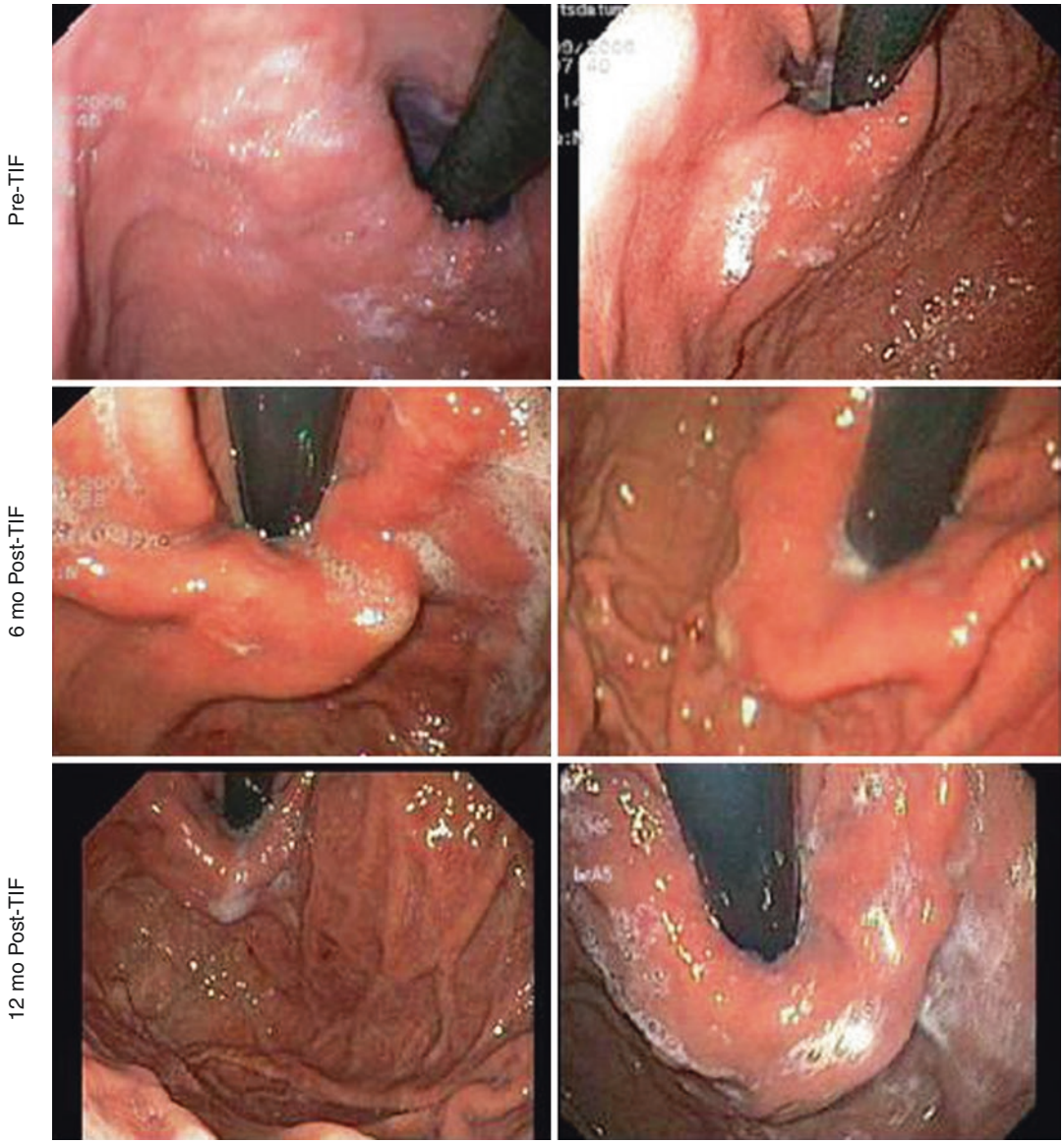


Fig. 95.11 Endoscopic images of gastroesophageal valves from two subjects before and at 6 and 12 months after TIF1 (Illustration from Cadiere et al. [24])

the Stretta® procedure, at 6 months, 58 % of Stretta® patients were off proton pump inhibitors, and an additional 31 % had reduced their dose significantly. In comparison, 97 % of laparoscopic fundoplication patients were off PPIs [35]. With long-term follow-up of these patients receiving the Stretta® treatment, beyond 2 years, 56 % had discontinued use of all antisecretory drugs [36].

This treatment has been reported in an uncontrolled study of a group of eight children with a variable follow-up period of 5–15 months [37]. It was reported that six out of eight children improved, and the cohort included three neurologically impaired children who also had concomitant PEG placement. One of this group had a postprocedure aspiration which was successfully treated. Of the two failures, one remained

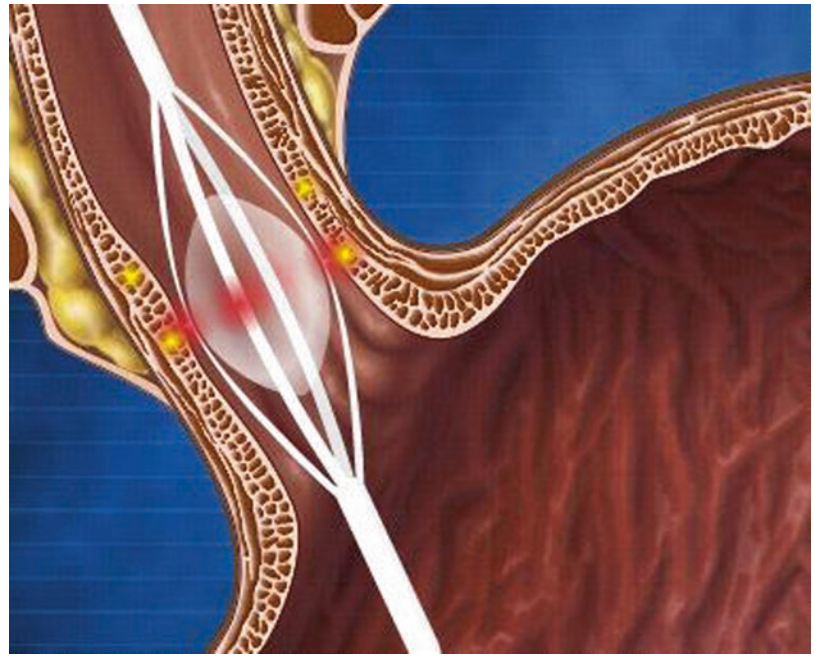


Fig. 95.12 The Stretta® system. The use of a balloon to deliver radiofrequency energy via needle electrodes to the mucosa

dependent on PPI and the other had a successful Nissen's fundoplication.

Pediatric gastroenterologists may be guarded in using this form of treatment as clearly using thermal energy treatment in a 70-year-old is different to a child who may have unknown consequences in the long term. Hence this is not recommended.

Gastroesophageal Biopolymer Injection

In the EnteryX® procedure, a liquid polymer is injected into the lower esophageal sphincter (LES) with a needle catheter via an endoscope. After the injection, the polymer solidifies into a sponge-like permanent implant. This improves the gastroesophageal junction, by supporting and improving its elasticity and therefore reducing the degree of gastroesophageal reflux (Fig. 95.13).

Cohen, in an international open-label clinical trial on 144 patients, showed greater than 50% reduction in PPI in 84% at end of 1 year and 72% by 2 years with elimination in 67% of patients [38]. In a prospective, randomized trial, endoluminal gastroplasty (EndoCinch®) was compared with EnteryX® in 51 consecutive patients dependent on proton pump inhibitor therapy. At 6 months, proton pump inhibitor therapy could be stopped, or dosage was reduced by more than 50% in 20 of 26 (77%) EndoCinch®-treated patients and in 20 of 23 patients treated by EnteryX® (87%, $p=0.365$). Approximately 25% of the patients in both groups required retreatment in an attempt to achieve symptom control. To date an estimated 3,800 patients have been treated with the EnteryX® device, which was approved in 2003 by the FDA. To date there are no published records of its use in pediatrics.

However, the FDA and Boston Scientific Corp. notified healthcare professionals and patients about serious adverse events, including death, occurring in patients treated with the EnteryX® device. Based upon reports filed with the FDA, patients suffered leakage, swelling, and ulcers in the esophagus. One elderly patient died after some of the polymer had been injected into the woman's aorta, which ruptured, causing her to bleed to death.

On September 23, 2005, Boston Scientific Corp. ordered a recall of all EnteryX® Procedure Kits and EnteryX® Injector Single Packs from commercial distribution. The com-

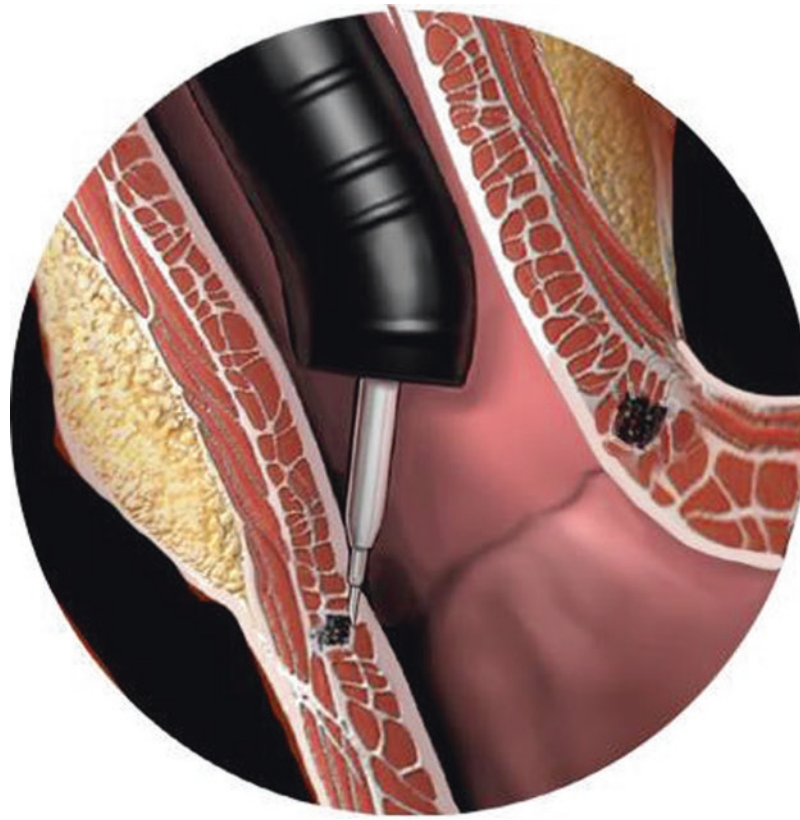


Fig. 95.13 Injection of liquid polymer into the esophageal mucosa. The EnteryX® procedure

pany's recall notice stated some doctors accidentally punctured the wall of the esophagus while injecting the substance, causing adverse events. Additionally, Boston Scientific Corp. recently suspended sales of its EnteryX® device after more than two dozen reports of problems. The notice was posted on the company's Web site, during the week of September 19, 2005 [39].

Summary

The most promising results seem to accrue in the midterm with the suturing devices which attain full-thickness plications, increase the intra-abdominal portion of the esophagus (most likely by plication tags inserting through the diaphragmatic crura as well as the full thickness of the esophageal wall, i.e., actual change in anatomy), and raise intra-sphincteric length and resting pressure. Endo-ultrasound may provide a more controlled and sophisticated approach to this technology in the future.

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Repair of Hiatus Hernia

96

Balgopal Eradi and Richard J. Stewart

Introduction

Hiatus hernia in children represents a heterogenous group of conditions, the common factor being protrusion of abdominal content into the chest via the oesophageal hiatus. It is the most common form of herniation of abdominal content through the diaphragm. Yet it does not find prominence in most textbooks of paediatric surgery. This may be because the commonest variety is almost synonymous with gastroesophageal reflux, and the other types are relatively rare. This chapter will deal with the different types of hiatus hernia in children in terms of aetiopathogenesis, epidemiology, clinical features, treatment and outcome. A few case studies are included to demonstrate the heterogeneity of hiatus hernia in children, and the operative strategies that may have to be devised to effectively deal with the problem.

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Anatomy of the Oesophageal Hiatus

The oesophagus enters the abdomen from the chest through an opening in the diaphragm – the oesophageal hiatus. Accompanying the oesophagus are the right and left vagus nerves, oesophageal branches of the left gastric artery and lymphatics of the lower oesophagus. Structurally, the diaphragm consists of a central tendinous portion into which circumferentially arranged muscle fibres attach. The crura are musculotendinous structures that anchor the diaphragm to the lumbar vertebrae and blend with the anterior longitudinal ligament of the vertebral columns. The medial fibres of both crura may arise from the median arcuate ligament which arches over the aorta as it enters the abdomen from the chest (Fig. 96.1).

The right crus is longer and broader and is attached to the anterior surfaces of the bodies and intervertebral discs of lumbar vertebrae 1–3 [24]. In the standard pattern, it passes cranially and anteriorly, dividing into a large right and smaller left limb which surround the oesophagus and decussate anteriorly before each attaching with the central tendon. The left crus is small and usually takes no part in the formation of the hiatus. It does, however, decussate with the right crus to the left of the oesophageal hiatus. Deviations from this standard pattern are common. The left crus may be completely separate and not

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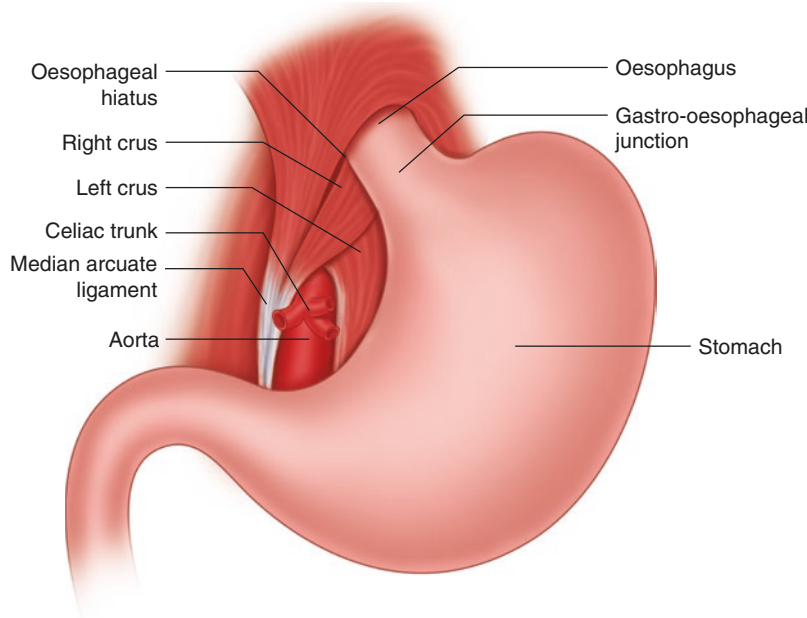

Fig. 96.1 Anatomy of the oesophageal hiatus and the gastroesophageal region

decussate at all with the right. Or it may provide increasing contribution to the formation of the oesophageal hiatus such that rarely, the hiatus is formed completely by the left crus [13].

Phreno-oesophageal Membrane

The phreno-oesophageal membrane has been described as a creamy-white layer that bridges the gap between the diaphragm and the oesophagus. It is an arrangement of elastic and collagenous fibres that derive from the peridiaphragmatic fascia and fan out to penetrate the distal 2–3 cm of the oesophageal muscle. It is thought to tether the distal oesophagus within the hiatal tunnel and maintain the oesophagogastric junction in its correct intra-abdominal position. The main component is formed by the fascia on the abdominal aspect of the diaphragm. This divides at the level of the hiatus into a thick inferior limb and a thin superior limb that passes upward to meet with the contribution from the endothoracic fascia. The membrane inserts into the oesophagus in layers of elastic fibres with small areolar spaces in between. Fat is absent in this structure [13]. Its elastic component allows the normal physiological movement of the lower oesophagus [63].

In infants, the oesophagus is firmly anchored by the phreno-oesophageal membrane as well as the thickened crus around the hiatus – sometimes called a "hiatal tunnel". Both the membrane and the "hiatal tunnel" become progressively attenuated with age [13].

Definition and Classification (Fig. 96.2)

The term hiatus hernia describes any form of herniation of abdominal content into the chest through the oesophageal hiatus. Sliding hiatus hernia, also called type I, refers to the presence of the gastroesophageal junction and a portion of the adjoining stomach in the mediastinum either transiently or continually [32]. In practice, however, the term hiatus hernia used in isolation is almost synonymous with the sliding variety.

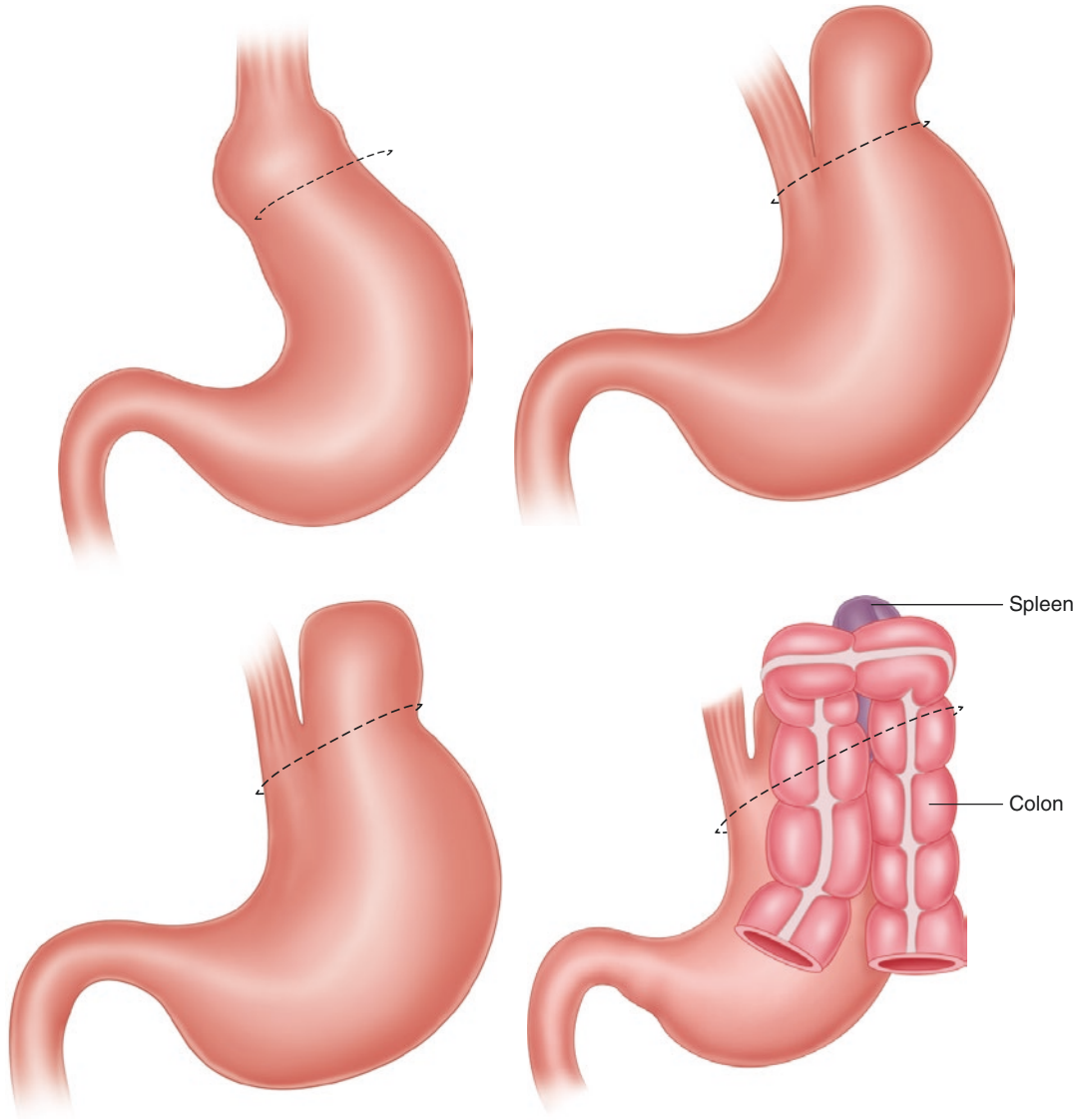

Fig. 96.2 Classification of hiatus hernia – a diagrammatic representation. Type I, sliding; type II, rolling; type III, mixed; type IV

In sliding hiatus hernia, the hiatal muscular tunnel is progressively enlarged and its normal slit-like configuration becomes a rounded opening. There is laxity of the phreno-oesophageal membrane, and this laxity determines the extent to which the stomach herniates into the chest. The membrane, however, is intact so that the herniated stomach is confined to the posterior mediastinum [40]. Initially, it is the extraperitoneal (bare) area of the stomach that is drawn upward, but as the condition progresses, the serosa-lined stomach is drawn in as well resulting in a peritoneum-lined sac. The sac is always empty except for the presence of the stomach [61].

Type II hiatal hernia is also known as paraoesophageal or rolling hiatus hernia. In this

defect, the gastroesophageal junction remains within the abdomen, usually held in place by fascia posteriorly and to the right toward the median arcuate ligament and the aorta. The gastric fundus forms the lead point and herniates into the chest alongside the oesophagus. The most common finding is to have the anterior wall of the fundus herniate into a ventral recess, anterior to the gastroesophageal junction. There is an associated defect in the phreno-oesophageal membrane or it is markedly attenuated. In older patients, the theory is that the pressure difference between the thorax and abdomen causes a progressive increase in the proportion of herniated stomach. The end result is that in time, the entire stomach herniates into the chest such that the pylorus and gastroesophageal junction are found in close approximation with organoaxial volvulus. This anomaly has been referred to as the "upside-down stomach" or type IIA [61]. In paediatric patients, however, there is little doubt as to the congenital nature of the defect, and an upside-down stomach may be detected at birth.

In most instances, as the type II defect progresses, the gastroesophageal junction becomes mobile as well and herniates through the hiatus into the mediastinum forming a mixed or type III hiatus hernia [61].

In type IV hiatus hernia, other abdominal viscera such as the small bowel, colon and spleen may be found within the chest [61].

Paraoesophageal hiatus hernia with more than a third to half of the stomach in the chest has been variously described as giant or massive paraoesophageal hernia [5, 25].

Antenatal Diagnosis

Congenital hiatus hernia has been diagnosed on antenatal ultrasound scans. Sonographic features that suggest the presence of hiatus hernia are (1) A hypoechogenic structure in the posterior mediastinum, anterior to the vertebral bodies and posterior to the heart. (2) The absence of mediastinal shift or pleural or pericardial effusion. (3) Abnormal location of the stomach which may be identified in a median position in the abdomen when it is partially herniated. If the stomach has herniated completely, the intra-abdominal gastric bubble may be absent. (4) The dynamic aspect of the stomach, i.e. its up-down movement through the enlarged hiatus into and out of the thorax. This last feature is considered the most helpful in the diagnosis. The differential diagnoses on prenatal ultrasound scans are oesophageal atresia and congenital diaphragmatic hernia [7, 19, 49, 57, 70].

Magnetic resonance imaging can help to confirm the antenatal ultrasound based diagnosis [57].

Genetics and Inheritance

Hiatus hernia in children as well as in adults is largely sporadic in incidence. However, familial incidence is well known. The incidence of sliding hiatus hernia in siblings of affected children has been estimated as being 10 % which is 20 times the estimated childhood population incidence of 0.5 % [67]. An autosomal dominant pattern of inheritance of sliding hiatus hernia has been suggested based on the identification of families in whom the condition occurs in numerous members over multiple generations [17, 18]. Though a genetic basis for severe gastroesophageal reflux disease in children has been suggested [50], no genetic basis has been identified for hiatus hernia, and despite numerous instances of familial clustering of both sliding and paraoesophageal hiatus hernia, no firm conclusion can be drawn as to the mode of inheritance [6, 22, 31, 55, 72].

There are reports of paraoesophageal hiatus hernia in the neonatal period associated with Marfan's syndrome [2, 35, 51, 52]. The hiatus hernia is the result of laxity of the ligamentous attachments of the oesophagus and stomach. Other connective tissue disorders like Ehlers-Danlos syndrome may also be associated with hiatus hernia [51]. Menkes disease, a rare disorder

of copper metabolism, has also been reported in association with hiatus hernia [60].

Embryology

The foregut is that part of the gastrointestinal tract that extends from the pharynx to the ampulla of Vater. As the foregut grows, a bulge appears which is destined to become the stomach. The diaphragm develops around the foregut, cephalad to the stomach. The dorsal and ventral mesogastrium in the region of the developing diaphragm forms the ligamentous attachment of the oesophagus to the diaphragm known as the phreno-oesophageal membrane. Variations in the length and fixation of this membrane allow abnormal mobility of gastroesophageal junction and are directly responsible for the occurrence of sliding hiatus hernia [43].

During development of the diaphragm, blind pouches form on either side of the dorsal and ventral mesogastrium extending into the mediastinum and communicating with the peritoneum. With the rotation of the gut, these peritoneal recesses come to lie anterior and posterior to the oesophagus. The recesses are described as being transitory, but their persistence may be responsible for paraoesophageal hiatus hernia. Thus this form is a hernia into a pre-formed peritoneal recess comparable to paracaecal and paraduodenal hernia [43].

Defective differentiation of the splanchnic mesenchyme has also been implicated in the aetiology of a paraoesophageal hiatus hernia. According to this theory, normal rotation of the midgut depends upon the position of the duodenum, which in turn depends on the normal development of duodenal musculature from splanchnic mesenchyme. The splanchnic mesenchyme also gives rise to the diaphragm around the foregut. Interference in the process of smooth muscle differentiation could result in both paraoesophageal hernia and associated malrotation [20].

Mixed hiatus hernias are likely to reflect a combination of laxity of the phreno-oesophageal ligament and persistence of peritoneal recesses [53].

Sliding (Type I) Hiatus Hernia

Incidence

Prior to 1951, only 93 children had been reported to have a hiatus hernia [14]. The diagnosis of hiatus hernia became much more prevalent consequent to evaluation of greater numbers of vomiting infants by contrast radiography. Carré estimated a childhood population incidence of 0.5 % [67]. However, the frequency with which sliding hiatus hernia is found depends upon the aggressiveness of the radiologist. Using abdominal compression, radiologists claim to be able to demonstrate a small hiatus hernia in 50–80 % of the adult population. It is believed that approximately 10 % of the adult population of North America will demonstrate a sliding hiatus hernia during barium swallow [61].

Presentation and Natural History

Carré has published the most comprehensive long-term cohort studies of infants diagnosed with hiatus hernia [14–16, 38]. His experience comprises 710 infants studied prospectively. Eighty patients have been followed up for more than 30 years. The initial presentation of sliding hiatus hernia in infants is by regurgitation or vomiting of feed. In Carré's series, 65 % of infants with symptomatic hiatus hernia become symptom free by 2 years of age without any treatment. This group of patients will improve clinically on weaning. Thirty-five percent of patients will worsen or fail to improve after weaning and will have troublesome reflux beyond the age of 4 years. Fourteen percent of patients who fail to improve on weaning will develop an oesophageal stricture if untreated.

If treated by postural therapy, 90 % will be free of symptoms by a year of age. About half the patients will have occasional heartburn as adults, though this is no more than the stated population incidence. The hiatus hernia will, however, continue to be demonstrable by radiological means in 40 % of patients after 20 years. Radiological resolution occurs by 4–6 years.

Though older children have poorer rates of resolution, 40 % will still respond to conservative measures.

Hiatus Hernia and Gastroesophageal Reflux

A competent gastroesophageal junction is essential to prevent gastroesophageal reflux. The functional integrity of the gastroesophageal junction has been attributed to numerous factors. A hiatus hernia has potential to cause disturbance to many of these. Progressive anatomical anomaly caused by the hiatus hernia results in decreased effect of the crural sling, straightening of the angle of His, loss of the abdominal segment of oesophagus and failure to maintain the lower oesophageal sphincter in the abdomen [39]. In addition, clearance of gastric acid from the oesophagus is impaired in patients of hiatus hernia [65]. This effect is particularly marked in patients who have non-reducing hiatus hernia [39]. The impairment in oesophageal clearance of acid in patients of hiatus hernia further accentuates gastroesophageal reflux-induced oesophageal mucosal injury [65].

The relationship of hiatus hernia with gastroesophageal reflux in terms of symptoms or complications is far from straightforward. As mentioned earlier, there are numerous patients who have a hiatus hernia without gastroesophageal reflux and vice versa. Hiatus hernia is therefore not an all or none phenomenon but a continuum of progressive disruption of the gastroesophageal junction. Large hiatus hernias are more significant clinically and are therefore more likely to require surgical intervention [39].

Diagnosis

Hiatus hernia is a radiological diagnosis made on contrast radiography. The indication to perform an upper gastrointestinal contrast series is prompted by symptoms attributable to gastroesophageal reflux that are "troublesome" or associated with complications [59].

The predominant radiological features that indicate the presence of a hiatus hernia are (1) a supradiaphragmatic lower oesophageal sphincter, (2) gastric mucosal folds above the hiatus, (3) a very wide hiatus or a wide portion of oesophagus above it and (4) a lateral notch representing the incisura angularis seen above the diaphragm [64].

The ability to make the diagnosis is dependent upon the experience of the radiologist, the use of adequate contrast and the time spent doing the study [36].

Management

The management of hiatus hernia is almost synonymous with that of gastroesophageal reflux disease which has been dealt with in detail in preceding sections of this book. The mere presence of a hiatus hernia does not alter management though it is more likely that the reflux and associated problems will fail to respond to conservative measures alone.

The indications for surgery are similar to those in patients of gastroesophageal reflux in the absence of a hiatus hernia and have been elucidated in previous sections.

Operative Treatment

The story of the evolution of modern anti-gastroesophageal reflux surgery from operations aimed at curing hiatus hernia is fascinating (Table 96.1). Over time, surgery to correct what was ostensibly an anatomical anomaly became one aimed at restoring the physiology of the gastroesophageal junction. Currently, reduction of the sliding hiatus hernia and narrowing of the hiatus, i.e. restoration of the anatomy of the oesophageal hiatus, are only a component of the overall procedure.

Congenital Paraoesophageal Hernia (Types II, III and IV)

Paraoesophageal hernias represent only 2–5 % of all hiatus hernias in series comprising adult patients [6, 41]. Paraoesophageal hernias that

Table 96.1 Evolution of antireflux surgery – a timeline

1579	Ambroise Pare	Descriptions of various types of diaphragmatic hernia [53]
1689	Lazarus Reverius	
1769	Morgagni	
1848	Alexander Bochdalek	
1836	Bright	First description of hiatus hernia [37]
1853	Bowditch	Three descriptions of paraoesophageal hiatus hernia included in a review of 88 cases of diaphragmatic hernia [66]
1895	Roentgen	Discovers X-rays [30]
1897	Rumpel	Observes contrast passing through the oesophagus [30]
~1900	Contrast radiography	First ante-mortem reports of hiatus hernia [12]
1919	Soresi	Describes operative repair of a paraoesophageal hernia [62]
1926	Akerlund	Coins the term "hiatus hernia" and provides a classification [66]
1928	Harrington	Describes operative correction of various hiatus hernias [27]
1937	Nissen	Reconnects a patient's oesophagus to his stomach following gastric resection for a perforated ulcer at the cardia. To reinforce his anastomosis, he mobilised the stomach and wrapped it around the oesophagus "in much the same manner as the rubber tube in a Witzel's gastrostomy" [47]
1951	Allison	Recognises that sliding hiatus hernia caused disturbance of the gastroesophageal junction leading to symptoms of gastroesophageal reflux. Devises a method for anatomical correction [3]
1942–1957	Belsey	Defines the technical principles of antireflux surgery – restoration of a competent valvular mechanism at the cardia rather than reduction of the internal hernia – "a physiological rather than anatomical solution" [11, 12]
1954	Barrett	Calls attention to other mechanisms, in particular the gastroesophageal angle, to prevent gastroesophageal reflux [10]
1955	Boerema	Describes anterior subhepatic gastropexy [68]
1956	Nissen	Describes similar procedure. Though initial results are encouraging, gastropexy in isolation is soon abandoned [48]
1956	Nissen	Examining the patient from 1937 16 years later, he noticed there were no subsequent symptoms of gastroesophageal reflux
		He adopts this method of wrapping the fundus of the stomach around the oesophagus to treat patients of hiatus hernia [47]
1977	Rosetti	Modifies Nissen fundoplication to obviate dysphagia and to preserve vagal innervation. The modification involved using only the anterior wall of the fundus for the wrap around the oesophagus and ensuring that this was done loosely [56]
1986	DeMeester	Further elucidation of the physiological basis of Nissen fundoplication. Advocates "short and floppy" fundoplication [23]

present in childhood or infancy are considerably rarer. Fewer than 130 patients have been reported in English language literature [1, 4, 6, 8, 9, 21, 26, 28, 30, 31, 33–35, 41, 42, 44–46, 54, 58, 69, 71]. Of these, nearly half are reported in a single series over 42 years from South Africa [41]. While it is very likely that there are numerous unreported cases, paraoesophageal hiatus hernia in infants and children remains a rare condition.

Presentation and Natural History

The average age of presentation based on reports in infants and children is around 2 years though symptoms may occur at any time after birth. There is no predilection for either sex; males and females are affected in equal measure. Unlike in sliding hiatus hernia in which there is physiological derangement of the gastroesophageal junction, most symptoms of paraoesophageal hernia

are mechanical in origin. The mass effect of the paraoesophageal hernia on the respiratory apparatus is responsible for its most common constellation of symptoms – respiratory distress and/or recurrent respiratory infections. An unusual noise in chest which may be exacerbated by feeding has also been described [34, 35, 54].

As the stomach herniates into the chest, the pylorus and gastroesophageal junction approximate each other and the greater curvature of the stomach rotates upward resulting in organoaxial volvulus. This may cause obstruction at the pylorus, gastroesophageal junction or both. Alternatively, obstruction may occur at the middle of the body of the stomach. Recurrent vomiting, which is usually non-bilious but may occasionally be bile-stained is the next most common mode of presentation.

In older children, presentation may be insidious with epigastric or retrosternal discomfort which may be related to feeds, nausea, dysphagia and occasional vomits. Diagnosis is often delayed due to the nonspecific nature of the symptoms.

A significant proportion of patients are anaemic. The anaemia is microcytic and hypochromic and represents chronic blood loss. The blood loss occurs due to reflux oesophagitis or due to ulceration of the inflamed, oedematous mucosa of the incarcerated stomach [34, 41].

Though patients may be quite ill due to respiratory infection and chronic malnutrition, catastrophic presentation with complete obstruction or strangulation and gangrene of the stomach has not been described in the paediatric age group.

Other features that have been reported include sweating, potentially due to vagal effect and self-induced vomiting.

Anomalies associated with paraoesophageal hernia are summarised in Table 96.2.

Table 96.2 Congenital paraoesophageal hernia – associated anomalies

GI
Malrotation
CVS
Ventricular septal defect
Right atrial isomerism
Pulmonary artery branch stenosis
Preduodenal portal vein
Left IVC
CNS
Posterior fossa cyst
Hydrocephalus
Microcephaly
Facial
Epicanthic folds
Hypertelorism
Cleft lip
Cleft palate
Miscellaneous
Ovarian torsion
Ear anomalies
Rocker bottom feet
Vertebral anomalies

Diagnosis

A chest radiograph is often the initial modality. Features of paraoesophageal hernia on plain chest radiograph are paracardiac opacity or air fluid level in the chest. The fluid level is seen behind the cardiac shadow on a lateral film. In the appropriate clinical setting, a plain chest radiograph may be all that is necessary to proceed to surgical correction. Differential diagnosis on plain chest radiograph includes congenital diaphragmatic hernia – usually right-sided, Morgagni hernia, eventration of diaphragm, lower lobe pneumonia, pleural effusion, pneumothorax, pneumatocele and bronchogenic cysts. Insertion of a nasogastric tube is helpful to differentiate a primary lung or thoracic condition.

Definitive diagnosis is by contrast upper gastrointestinal series. The contrast study will conclusively demonstrate the herniation of the stomach into the chest. It is often difficult however to ascertain the exact location of the gastroesophageal junction and the orientation of the stomach. Sometimes, the sac may be empty or may only contain omentum at the time of the contrast study, and this may confound the diagnosis.

CT of the chest and abdomen has been used to gain additional anatomical information [9], but generally, cross-sectional imaging does not contribute to the management [30, 41].

Management

It is generally agreed that surgical intervention is warranted as the condition is likely to progress, and there is no likelihood of spontaneous resolution.

Due to alteration of the anatomical relations of the hiatus, oesophagus and the fundus of the stomach, the physiology of the gastroesophageal junction is affected resulting in gastroesophageal reflux in nearly 2/3 of patients following repair of the hiatus hernia alone [41]. A concomitant anti-reflux procedure is therefore advisable though some would debate this [29].

Some authors also recommend gastropexy either by fixation of the fundus posteriorly or by Stamm gastrostomy to decrease the chance of recurrence [34, 35].

Results

In series that have reported a reasonable length of follow-up, the overall results are good. Mortality has been reported in four patients. Three neonates from a single series [35] died due to multiple associated anomalies, pneumonia secondary to neonatal Marfan's syndrome and fungal sepsis. A 4-month-old with compromised lungs due to recurrent aspiration died postoperatively due to pneumonia and the resulting sepsis and respiratory insufficiency [33].

Recurrence of the paraoesophageal hernia has been reported in three patients, none of whom had a gastropexy at the initial operation [35, 71].

The most common complication reported is intestinal obstruction due to adhesions, reported in eight patients overall [35, 41].

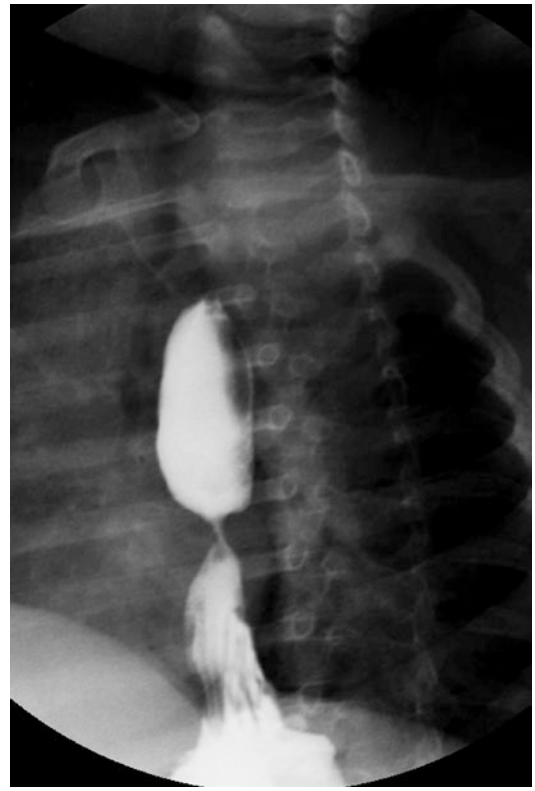

Fig. 96.3 Contrast swallow demonstrating an oesophageal stricture and hiatus hernia

Case Studies

Sliding Hiatus Hernia Complicated by Oesophageal Stricture

A 13-month-old child was referred with progressive difficulty in feeding for 4 months having been treated conservatively with gastroesophageal reflux from the age of 3 months. Contrast swallow was performed which revealed a hiatus hernia and an oesophageal stricture (Fig. 96.3). A laparoscopic Nissen fundoplication with concomitant oesophageal dilatation was performed. A "short and floppy" wrap was created over a bougie. As the operation has been described in detail in preceding chapters, it will not be further elaborated upon here.

Following the operation, the child has been free from symptoms.

Type III Hiatus Hernia in Newborn

A newborn baby was transferred to us with failure to tolerate any feeds due to vomiting and associated choking episodes. The symptoms prompted a contrast upper gastrointestinal contrast series (Fig. 96.4) which showed the entire stomach had herniated into the chest.

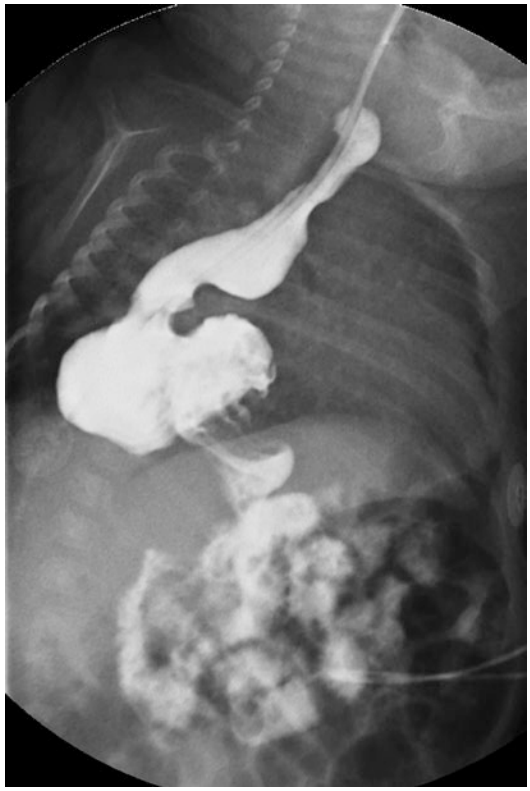

Fig. 96.4 A previously unreported neonate with herniation of the entire stomach into the chest. The pylorus and proximal duodenum are clearly seen in the chest

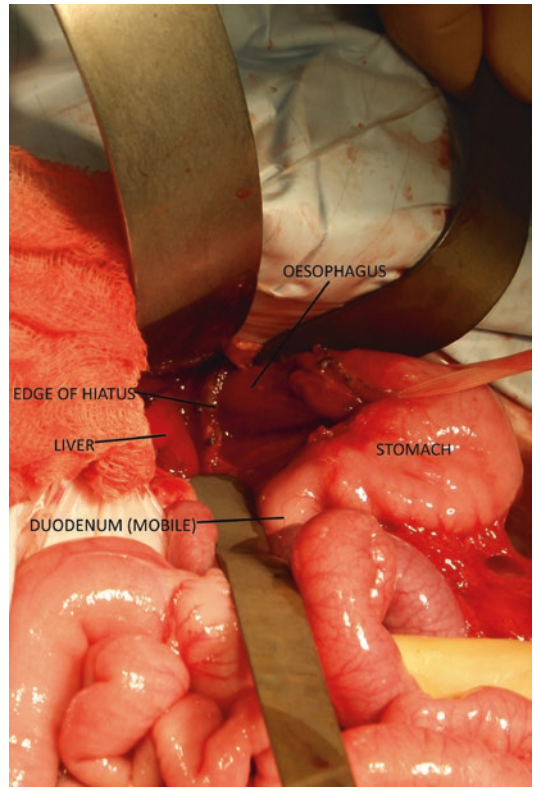

Fig. 96.5 Operative photograph after reduction of stomach from the chest. The sac has been excised to delineate the hiatal defect

Laparoscopic repair was attempted but had to be converted to open procedure. Dilated bowel loops resulted in paucity of space and poor visibility. A left upper transverse incision was used to gain access to the upper abdomen.

The left triangular ligament of the liver was divided, and the left lobe of the liver retracted out of the way to enable a good view of the oesophageal hiatus. The stomach was delivered out of the chest. There was no difficulty in reducing the contents of the hernia which is in keeping with the experience of other authors [41, 69]. With gentle traction on the stomach, the peritoneal sac is evaginated and the peritoneal reflection divided. The dissection is continued to divide the most superficial layer, taking care to avoid the vagus nerves. The sac was gradually dissected free and excised as much as required to permit a good view of the edges of the hiatal defect (Fig. 96.5). The hiatal defect was then loosely approximated posterior to the oesophagus. A large nasogastric tube was placed within the oesophagus to ensure that the hiatal repair is not too tight.

The author's preference is to use nonabsorbable suture (Gore-Tex^{tm} 3-0 or 2-0 depending on the age and size of the child). Interrupted sutures were placed taking good "bites" of the edges of the hiatus which are then loosely approximated. The stitches are placed taking variable thickness of the muscle to avoid separating the muscle fibres.

A posterior 270° fundoplication and Stamm gastrostomy were also performed.

Postoperative recovery was uneventful. Currently, the child is thriving and asymptomatic. As he is feeding well orally, his gastrostomy tube has been removed.

Hiatus Hernia Around a Gastric Pull-Up

A 3-year-old child with pure oesophageal atresia, who had a gastric pull-through at another institute, was admitted with worsening respiratory distress. A chest X-ray revealed herniation of the bowel into the chest (Fig. 96.6).

Herniation of the small bowel into the chest through the oesophageal hiatus was confirmed on laparoscopy. It was possible to reduce the herniated bowel and define the edges of the hiatal defect laparoscopically (Fig. 96.7a). The edges of the defect were then approximated to the wall of the duodenum which was seen entering the oesophageal hiatus. Gore-Tex 3-0 was used and the knots were tied intracorporeally (Fig. 96.7b).

Postoperative recovery was uneventful and there have not been any subsequent problems.

Large Hiatus Hernia Secondary to Congenital Diaphragmatic Hernia

A term baby with antenatally diagnosed congenital diaphragmatic hernia underwent repair of the posterolateral Bochdalek-type diaphragmatic defect after a difficult period of preoperative stabilisation. Postoperatively, the child failed to tolerate feeds. A repeat upper gastrointestinal contrast series demonstrated a large hiatus hernia and duodenal obstruction (Fig. 96.8).

As the large hiatus hernia secondary to congenital diaphragmatic hernia was not likely to resolve, the patient underwent operative correction. Laparotomy was performed via a left upper abdominal transverse incision. The stomach was

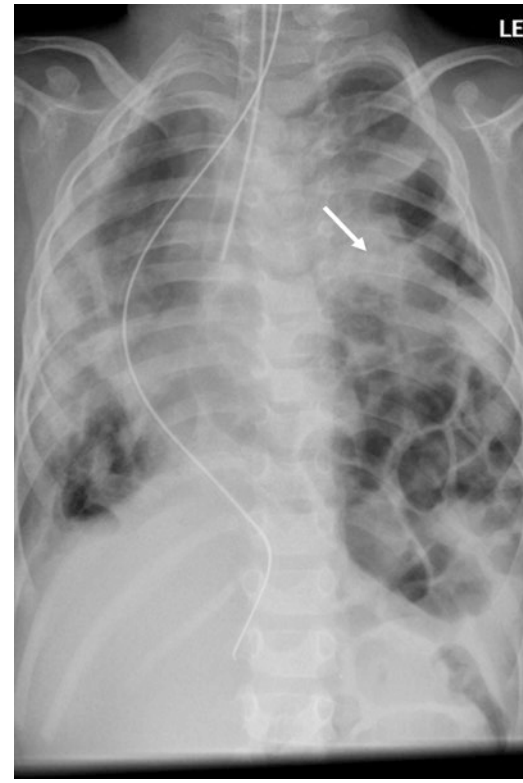

Fig. 96.6 Herniation of the small bowel (*arrow*) into the chest via the oesophageal hiatus, around the gastric pull-up

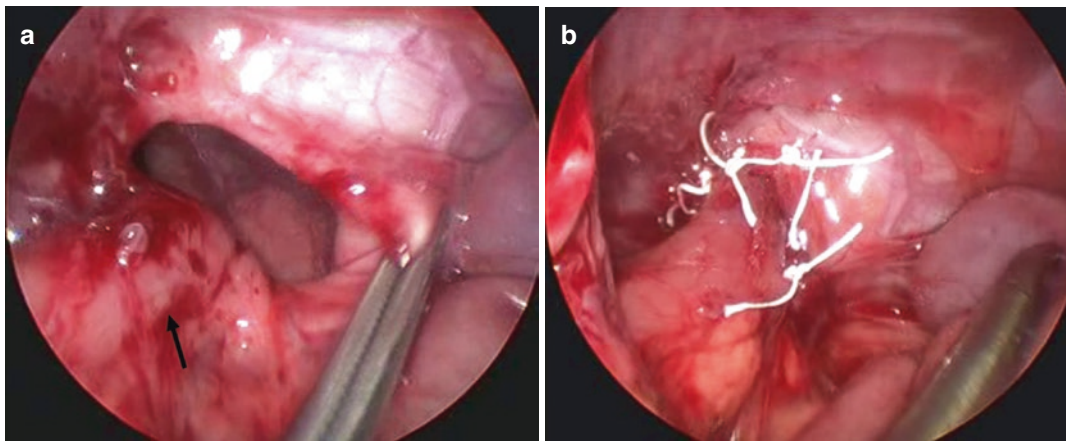

Fig. 96.7 (**a**) Laparoscopic view of the large hiatal defect. The stomach is seen entering the hiatus (*arrow*). (**b**) The edges of the hiatus have been approximated to the wall of the stomach to preclude further herniation of abdominal content

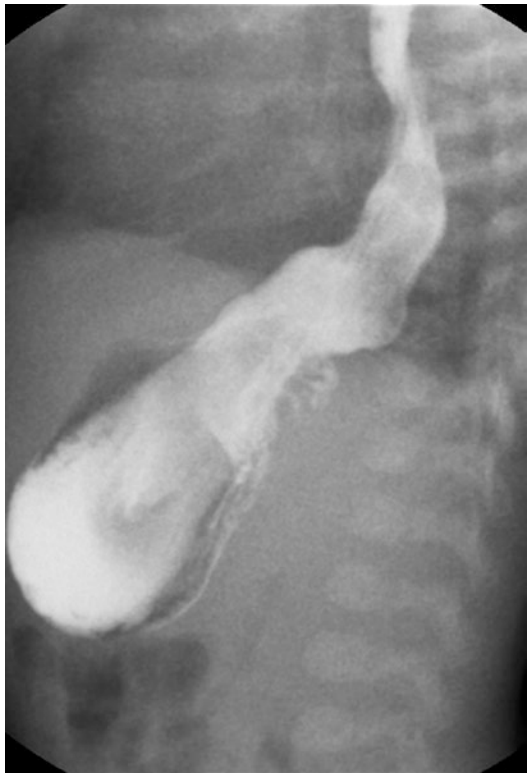

Fig. 96.8 Large sliding hiatus hernia following repair of congenital diaphragmatic hernia, demonstrated on upper gastrointestinal contrast series

mobilised to gain a length of intra-abdominal oesophagus. The hiatal edges were approximated loosely around the lower oesophagus. A posterior 180° fundoplication and a Stamm gastrostomy were also done. The duodenal obstruction was relieved by dividing adhesions. Following this, the baby made an uneventful recovery and is currently doing well.

Conclusion

Hiatus hernia in infants and children represents a diverse group of disorders with marked difference in presentation, treatment and outcome. Marcel Bettex, among others, considered all these to be a continuum of worsening pathology from gastroesophageal reflux without hiatus hernia, a condition he and others term "chalasia" to herniation of the entire stomach and organoaxial volvulus (upside-down stomach) [12].

Others such as Carré, who have also studied the natural history of these disorders, have not demonstrated such progression [14, 38]. Indeed, adults with type I or sliding hiatus hernia do not seem to develop large mixed or type III hernias over time. Also, if type III hernias always progressed from type I hernias, then in theory, type II or rolling hernia, in which the gastroesophageal junction remains within the abdomen, should never occur. Karpelowski et al. who have published the single largest series of paraoesophageal hernia did not observe sequential progression either [41].

That the defect is congenital in at least some individuals is beyond doubt due to the antenatal and neonatal diagnosis of paraoesophageal hiatus hernia. Whether the paraoesophageal hernia seen in adults represents the same condition or is a separate, acquired one is not clear at present. Certainly, it would be interesting to study the effect on the incidence of the condition in later years of life once antenatal diagnosis becomes more widespread and accurate.

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97 Endoscopic Treatment of Benign Esophageal Strictures with Removable or Biodegradable Stents

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Introduction

Although pediatric literature on esophageal stents is limited, there is substantial literature on this topic in adults. The main indication in adults is palliative therapy in patients with unresectable esophageal cancer, but stenting in adults is also used for the management of benign conditions such as esophageal fistulas, leaks, perforation, and benign strictures. The major pediatric indication is refractory or recurrent esophageal stricture, followed by tracheoesophageal fistula, esophageal perforation, and anastomotic leak [1]. Esophageal strictures in children are most frequently the consequence of esophageal atresia, ingestion of caustic (alkaline) products, or a consequence of gastroesophageal reflux disease. Management of esophageal perforation may be another indication.

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Treatment of Esophageal Strictures in Children

Repetitive dilatations are the standard therapeutic approach of esophageal strictures [2]. The younger the child, the more balloon dilatations are considered standard care. In older children, Savary-Miller dilatators are more frequently used, similar as in adults. The role of high doses of steroids in the prevention and treatment of esophageal stenosis and in the mechanism of scar formation (mainly caustic injury) is still heavily debated [2]. Systemic high doses of methylprednisolone (1 g/1/73 m [2]) have been advocated to reduce the number and the severity of the strictures [3]. However, early treatment (within 24 h after ingestion of the caustic product) versus delayed treatment or short versus long treatment (less than or more than 21 days) was reported to make no difference [4].

Topical application of mitomycin has also been applied with some success (about two thirds) in the treatment and prevention of scar formation [5, 6]. Esophageal resection and colon interposition or gastric pull-through is proposed in the most severe, relapsing cases [7, 8]. After a median follow-up of 33.3 (11–41) years, 23 (43 %) of 53 individuals experienced mild symptoms of reflux; scoliosis, 12 (22 %) of 53; and/or other complications, 15 (27 %) of 53 required further surgery [7].

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The Use of Stents in Benign in Esophageal Strictures

Clinical experience with stents is mostly derived from adults with esophageal cancer, but with the development of new types of stents, more and more stents are placed to treat benign conditions.

Various manufacturers provide different types of stents. They differ in stent material, design, luminal diameter, radial force exerted, flexibility, degree of shortening after placement, and extent of coverage. Every stent type has its proper characteristics with advantages and disadvantages. It is important to recognize not only the benefits but also the shortcomings and complications of the various stents before deciding to insert a stent in a patient. Currently, self-expandable plastic stents (SEPs) and self-expanding metal stents (SEMs) mostly made from nitinol (alloy of nickel and titanium) dominate the market because of their removability (SEPs) or because of their ability to conform to anatomical angulations (SEMs) [1].

Self-Expandable Metal Stents

The first expandable stents available were uncovered and were made of stainless steel. These stents had the advantage over the classical plastic prostheses in the way that they were only 3 mm in diameter before deployment, which made the insertion easier, and dilatation of the stricture prior to the stent insertion was often not necessary. After expansion, stent diameter increased to 16 mm [9]. The newer stents are made of nitinol and have a diameter up to 23 mm after expansion [1]. Nitinol is a biocompatible alloy with a shape memory and high elasticity. Nitinol stents are flexible, are highly kink resistant, and exert a low chronic radial outward force, which makes them very attractive to manage cancer strictures.

Although the palliation for dysphagia caused by esophageal cancer was not better, in most studies, the complication rate of SEMs was significantly lower than with the plastic prostheses [10]. Major complications of SEMs comprise hemorrhage, aspiration, perforation, food impaction, and migration with sometimes bowel obstruction. Early minor complications include chest or throat pain, nausea, fever, and reflux. Stents that are close to the upper esophageal sphincter induce a high degree of intolerance due to pain and globus sensation, as well as an increased risk of complications such as tracheoesophageal fistula and aspiration pneumonia. Therefore, it is recommended to put a stent at least 2 cm below the upper esophageal sphincter. In the long-term, ingrowth of tumor in the uncovered stents is a problem [11]. Thus, covered SEMs were developed. In fact, these covered stents were only partially covered, allowing the uncovered part embedding and anchoring in the mucosa. In adults with malignant esophageal stenosis, covered SEMs are reported to be preferable to uncovered stents because there is less recurrent dysphagia due to tumor ingrowth and obstructing mucosal hyperplasia. On the other hand, there is a trend to have more migration with covered stents [10, 12].

Experience in the use of SEMs in benign strictures is by far more limited than in malignancy. Several limitations of SEMs preclude their routine use in benign esophageal strictures. The most important reason not to use SEMs in benign strictures is their difficulty in removing them because of tissue embedment that occurs in the uncovered portion. Traumatic removal results in complications such as bleeding, but also the development of new strictures at the site of injury caused by tissue granulation. Moreover, SEMs placed for benign disease are associated with significant other complications such as high migration rates, fistula, erosion into vital structures, and even death [13]. Stent migration is more likely to occur with covered than with uncovered stents. Based on the high complication rate, partially covered SEMs in their current form cannot be recommended for treating benign esophageal stenosis [1].

Self-Expandable Plastic Stents

This type of stent is made of polyester netting embedded in a silicone membrane. The proximal end of the stent is flared in an attempt to prevent

distal migration. The upper and lower parts of the polyester mesh are covered with silicone to prevent tissue damage and thus granulation. The diameter of the delivery device is 12–14 mm, which makes dilatation before stent insertion mandatory. Similar to SEMs, the stent should cover the whole length of the structure with an additional 1–2 cm above and below the stricture. Retrieval and repositioning of this fully covered stent can be done with a foreign body forceps or a standard polypectomy snare [1].

SEPs have been shown to be efficient and safe in the management of malignant esophageal strictures. Success rate of insertion is high (>90 %), and in most patients, dysphagia improves. Major complications include stent migration, food impaction, bleeding, and death. Tumor ingrowth does not occur, but tumor or hyperplastic overgrowth was observed in a significant proportion of patients. Minor complications include chest pain, nausea, fever, and reflux [14, 15].

Trials comparing SEMs to SEPs demonstrate that the stents are equally effective in palliating malignant obstruction, but SEMs are associated with significantly fewer complications, especially migration, than SEPs [16].

SEPs are increasingly used to treat benign esophageal disease including strictures, fistulas, anastomotic leaks, and perforations. Advantages of SEPs over SEMS in benign esophageal disease include the option of retrieval, limited local tissue reaction, which might limit the formation of new strictures, and lower cost. Up to now, there are no large RCTs evaluating the role of SEPs in benign esophageal strictures, but there are several case series. Initial results were very promising with relief of dysphagia in a high number of patients (up to 95 %), not only during stenting but also after removal of the stent [17]. In more recent series, however, the long-term success rate was far lower (17–30 %). Moreover, the complication rate was high in some series, including food bolus impaction, stent migration, severe pain, hemorrhage, perforation, and death [18, 19]. A pooled-data analysis from ten studies including 130 patients who were stented for benign esophageal strictures showed a favorable risk/benefit [20]. This study supports the idea that SEPs could be a valuable alternative to repeat endoscopic dilatation for benign disease before referring patients to surgery.

Fully Covered, Retrievable SEMs

Fully covered retrievable SEMs have been developed and approved for malignant disease, but they are theoretically also promising for treating benign disease. The stent is composed of a nitinol wire covered with polyurethane. Nylon loops are woven into the ends; they can be grasped with a forceps, which will narrow the stent and make retrieval easier and less traumatic. Moreover, a specific stent retrieval system has been designed [1].

Some small series reported that the stents relief dysphagia in most patients with benign esophageal strictures. Stents were removed after 8 weeks. However, stent migration was frequent (up to 80 % at 8 weeks), and new/recurrent stricture formation was seen in about 50 % [21, 22].

Recently, a stent that is fully covered internally but not externally has been developed. It is postulated that this kind of stent will migrate less. The first data with this stent are promising, but only few patients have been treated for benign strictures.

Prospective data from RCTs are needed before general recommendations on the use of fully covered retrievable stents can be made.

Biodegradable Stents

A recent evolution is the development of biodegradable stents. This type of stent is made of degradable synthetic material. The stent integrity and radial force is maintained for a period of 6–8 weeks following implantation. Stent disintegration occurs 11–12 weeks after insertion. Dual flared ends reduce the risk for migration. In a Japanese case series, stent migration was observed in 77 % of 13 adult patients. However, no symptoms of restenosis were observed, and further endoscopic therapies were not required [23]. More data are needed before the use of these stents can be recommended.

Pediatric Experience

The number of pediatric studies is very limited. And all reports are retrospective, have small number of patients (or are case reports), and use a wide variety of stenting techniques. As a consequence, close collaboration with an experienced adult gastroenterologist is recommended.

In Turkey, surgical placements of stents for corrosive esophageal structures have been introduced already in 1989. Stenting provided a much better outcome, leading to a healing in 68 % of the patients compared to 33 % with the "classic" therapy (dilatations). Poor patient compliance and GER resulting from esophageal shortening of the esophagus during scar formation were the most important reasons for failure of the stenting [24]. Another Turkish series reported a series of 11 patients with esophageal stents in 10 years time [25]. Eight patients had a normal feeding pattern, also after stent removal, with a mean follow-up of 3.5 years after stent removal. Long-term stenting was suggested to decrease the need for surgical reconstruction and to decrease esophageal stricture incidence. The Turkish experience regards "closed stents," which means that the food needs to pass between the esophageal mucosa and the stent, comparable to the effect of a large nasogastric tube.

A Chinese series of 33 patients suggested laparotomy to bring the esophageal stent in place 2–3 weeks after ingestion or even immediately in case of esophageal perforation [26]. In this series, 18 children (1–14 years) were included. The stent was constructed from a silicone rubber tube of 10–12 mm inner and 14–16 mm outer diameter with a length of 40–60 cm. A catheter was fixed to the proximal end of the stent as the distal end of the stent was used as a gastrostomy. Stents were removed after 4–6 months. The results were excellent as 85 % of patients had normal food intake 3 months after stent removal. This kind of stenting is however not comparable with the new less invasive techniques.

A SEPs (Polyflex/Rüsch) was inserted in ten patients between 6 months and 23 years with benign esophageal stricture, mostly after corrosive ingestion [27]. All patients were previously included in a dilatation program without success. Stents were placed over the stenotic area after performing a dilatation. Fifty percent of the patients received one stent; the others needed two or more stents because of restenosis. Stents were left in place from 20 to 133 days. Five patients were completely cured; others needed further stent treatment. The children experienced nausea and vomiting during several days after placement of the stent. These episodes were related to the length of the stent. Treatment with midazolam and ondansetron reduced the symptoms. Pain relieving medication was required during the first days after stenting. Patients also needed acid blocking medication while the stent was in place. Since the stent results in a constant "open" esophagus, often with the stent also dilating the lower esophageal sphincter, it is logic that there is increased reflux. Long-term tolerance of the stent was most of the time excellent and stents allowed the children normal feeding.

Fully covered tracheobronchial stents were endoscopically placed under general anesthesia in seven pediatric patients (6 months to 7 years old) with benign esophageal conditions [28]. All patients had several unsuccessful dilatations before stent placement. Balloon dilatation was performed before stent insertion. The diameter of the stent was selected according to the age and estimated esophageal diameter; the length was chosen in order to provide 2 cm of stent on each side of the stricture(s). In some patients, serial stents with increasing diameter were inserted. Stents were removed between 3 and 15 days without complications by using a forceps. As stents were left in place longer, it was more effective. Six of seven patients did benefit from the stenting. There were no complications during placement. One patient did not benefit from esophageal stent placement, because the stent migrated downward (ad). One patient had some gagging, which led to early removal of the stent, and the stent was removed in emergency in one patient for respiratory distress.

Zhang and colleagues reported on their experience with covered retrievable expandable nitinol stents in 8 children with corrosive esophageal stenosis [29]. The stents were placed in all patients without complications and were success-

fully removed 1–4 weeks after insertion. After stent placement, all patients could take solid food without dysphagia. Stent migration occurred in one patient; in this patient, the stent was repositioned. During the 3-month follow-up period after stent removal, all children could eat satisfactorily. After 6 months, two children required balloon dilatation (three times in one and five times in the other).

The first two cases of successful implantation of a biodegradable stent in children with caustic esophageal stricture were performed in Minsk, Byelorussia, in 2006. However, this experience was not reported in international literature. We reported a positive experience with an SX-Ella biodegradable esophageal stent in a child [30]. A major advantage of this stent is the fact that it remains in place for 6–12 weeks and that it must not be removed endoscopically. A drawback is that this stent is currently only available in large diameter and cannot be inserted in small children. As the stent is degraded by acid, PPIs must be administered to prevent early degradation.

Discussion and Conclusion

The major indication for esophageal stenting is malignant disease in adults. Extrapolation of the experience in this patient group to children with benign esophageal disease is impossible. There has been increasing interest in the use of stents in benign disease. Data on the use of SEMs and SEPs in the management of refractory benign esophageal strictures have been mixed. Until there is significant improvement in the design, these stents cannot be routinely recommended for this indication. The use of self-expandable stents for the management of anastomic leaks and perforations seems promising. The development of removable, fully covered stents increases the potential uses for stents in children expanded to include treatment of a wide variety of congenital and acquired esophageal strictures [31]. However, long-term prospective data obtained from controlled trials on the use of retrievable SEMs and biodegradable stents in the management of benign esophageal lesions are awaited. In the mean time, stents may offer a solution to some children with recurrent or chronic benign esophageal stricture. Since experience in children is (still) very limited, it is evident that esophageal stenting in children should be performed in referral centers.

First-line treatment of esophageal strictures remains endoscopic dilatation, followed by mitomycin application [2]. When these measures fail, stenting of the stricture is a valuable option. The timing of stenting is uncertain, but there are some indications that early stenting could be beneficial in certain circumstances [26]. A clinical trial comparing early stenting with repeated dilatation could answer this question, but will be extremely difficult to perform in such a rare condition. Likelihood of success seems most dependent on the ability of the patient to tolerate initial placement of the stent without complication and maintaining proper positioning for an adequate period of time before removal [31].

In small children, adult stents with a large diameter cannot be inserted because this causes prolonged pain and nausea. There are some other possibilities, including tracheobronchial and custom-made stents. Tracheobronchial stents have a smaller diameter, but they are stiffer and have a higher radial force. The advantage is that these stents deploy immediately. The disadvantage is that they may be more traumatic and less easy to remove. Custom-made stents are probably a better choice. These stent are made for the individual patient with the diameter and length adapted to the patient. Moreover, the upper and lower part can be made wider, if desired the stent can be partially uncovered and anti-migration flaps can be included; all of these will reduce the migration rate, which remains a major concern in benign disease. Indeed, as dilatation of the stricture is successful, migration rate increases.

Another point of discussion is the duration of treatment. In general, covered stents are removed after 1–4 weeks. It has been shown that results are better when stents are removed after more than 1 week [28]. The longer a stent remains in place, the higher is the risk of migration, the higher the chance of in- or overgrowth, and the more difficult it is to remove. A logical approach

would be replacement of the stent by a stent with a larger diameter (e.g., +2 mm) every 2 weeks until the desired diameter is reached [28].

Removal of a fully covered stent, which is designed to be removed endoscopically, is usually quite easy. Extraction involves using an alligator or rat tooth or biopsy forceps, to pull the purse-string suture into the endoscope channel, thereby collapsing the top of the stent [1, 28]. If impossible to grab the upper string suture, one can grab the lower one and pull the stent into the stomach before extraction. If the stent cannot be pulled into the biopsy channel, an overtube or endotracheal tube can be used [28]. Complications after stent removal are infrequent, but it is advised to remove stent under anesthesia with endotracheal intubation.

Although recommendations cannot be made based on evidence, it seems to the authors that esophageal stenting should be given a chance after failure of dilatations and mitomycin application, but before colon interposition. Knowledge of different types of stents and complications is essential, and stents are preferably inserted in experienced centers. At present, retrievable covered SEMs, if possible custom made, might be preferable, but RCTs are awaited before strong recommendations can be given.

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Oesophagogastric Dissociation: When Is It Relevant?

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A. Bianchi and A. Morabito

Oesophagogastric Dissociation

The Clinical Situation

Even for the otherwise normal child, clinically significant gastro-oesophageal reflux may be a cause of major morbidity and possible mortality and effective treatment difficult to achieve. Despite heavy medical management, the patient's quality of life and indeed that of his family or caregivers is often severely reduced and an outwardly effective conservative approach may not always be acceptable. Failure of conservative management often leads to a surgical antireflux procedure. Of the several varieties of fundoplication, for which the eventual long-term outcomes are not much different, the Nissen 360° moderately loose wrap, undertaken through an open upper abdominal approach or laparoscopically, is still the more common intervention. Fundoplications in this setting have proven generally satisfactory, although for a minority the wrap may loosen and reflux recurs or a hiatal hernia may appear.

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For mentally impaired children and particularly those with pharyngeal neuromuscular incoordination, however, a satisfactory result is much more difficult to achieve. They suffer significantly from difficulty with swallowing and are markedly prone to saliva and food aspiration with pneumonitis and frequent hospitalisation for 'chest infections'. In addition the inability to take an adequate oral intake, the significant gastro-oesophageal reflux, and the pronounced retching and vomiting lead to poor nutrition and failure to thrive. The inevitable 'mess around the child' leads to reluctance to physically handle the child, with consequent emotional deprivation both for the unhappy child and for the unfortunate family. The constant attention demanded by these children places a great strain on the parents' relationship and impacts also on the siblings.

Such mentally impaired children often first come to surgical attention at an advanced age with a referral from their paediatrician for a feeding gastrostomy, the presence and repeated passage of a nasogastric feeding tube having become a major problem. Although advocated by some, placement of a gastrostomy tube alone will aggravate the gastro-oesophageal reflux in well over 50 % of children. If the child's overall condition does not allow for a safe concomitant antireflux procedure, then a temporary transgastric jejunal feeding tube/button or a tube jejunostomy is a better prospect. A fundoplication, if the child's condition permits, is a consideration

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although it must be realised that mentally impaired children are prone to a significantly higher incidence of breakdown of the wrap with recurrent reflux (7–35 % within a 2–5-year period). Repeated surgery may be hazardous with increased morbidity and is unwelcomed by the family and also by the medical caregivers who must manage these frail, physically compromised children with impaired respiratory function.

Faced with this situation and asked to express a preference, these concerned and weary families will often ask for a single operative intervention without risk of recurrence of reflux or of further surgery, which will resolve the majority of their feeding and respiratory problems, will allow adequate nutrition and growth and will reduce hospitalisation episodes. Oesophagogastric dissociation [1] (OGD) with gastrostomy is designed to specifically meet these essential needs by eliminating gastro-oesophageal reflux and the possibility of its recurrence and allowing for enteral nutrition without loss. OGD, however, does not alter the pharyngeal incoordination and the potential morbidity from aspiration of saliva, nor does it resolve the troublesome centrally coordinated retching.

Preoperative Evaluation and Preparation

Surgical options for these children are often a later consideration, and by the time of first surgical referral, the child has been fully investigated and the need for help is obvious. Videofluoroscopy, pH studies, radioisotope scans and contrast studies will have confirmed the clinical scenario of a mentally impaired child who is failing to thrive because of inability to swallow, marked vomiting and gastro-oesophageal reflux, with saliva and food aspiration and frequent pneumonitis confirm the severity.

For the perioperative evaluation, delayed gastric emptying, the possible presence of an oesophageal stenosis or ulceration are all pertinent to the surgeon, while lung function is of most concern to the anaesthetist. The services of a paediatric respiratory physician and an intensivist are appropriate to ensure that the child is in the best condition for the planned surgery, and a period of preoperative intensive respiratory management, physiotherapy and parenteral nutrition could be invaluable in reducing the postoperative morbidity. Perhaps the most effective preparation for surgery is the recruitment of a multidisciplinary team to address the specific needs of the individual child and family.

It is the surgeon's specific duty to become personally involved with the family or caregivers through in-depth counselling sessions such that the family's concerns are fully addressed. There should be no doubt as to their clear understanding of the proposed surgery exploring all possible risk, potential postoperative morbidity and *the family's expectations*. The family must be fully aware that OGD is designed to eliminate reflux and food aspiration, to improve lung function and to allow stable nutrition and growth but that it will not address the swallowing difficulty, saliva aspiration and the centrally mediated 'retching' that is often so distressing to the family.

The Operative Procedure

Through an upper abdominal approach, the left lobe of the liver is displaced medially to allow liberal mobilisation of the oesophagus at the hiatus in the diaphragm (Fig. 98.1). The posterior vagus nerve is protected, the oesophagus is detached at the cardio-oesophageal junction and the stomach oversewn, leaving access only through a gastrostomy. The jejunum is divided and the distal end is passed in Roux-en-Y isoperistaltic fashion on a tension-free mesentery through the transverse mesocolon and behind the stomach, to anastomose with the oesophagus at the level of the diaphragm. A 'wide oblique' rather than a circular end-to-end anastomosis will reduce any possibility of stenosis. Bowel continuity is established by end-to-side jejunojejunostomy at a point 40 cm distal to the oesophageal anastomosis. A pyloroplasty is added if there has been a possible pre- or intraoperative

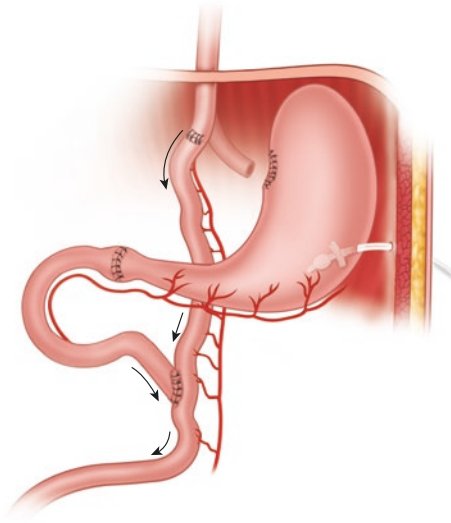

Fig. 98.1 The oesophagus is detached at the oesophagogastric junction and anastomosed to an isoperistaltic jejunal Roux loop. An end-to-side jejunojejunostomy at 40 cm from the oesophageal anastomosis, a gastrostomy and a possible pyloroplasty complete the procedure

injury to the vagus nerves or preoperative evidence of delayed gastric emptying. Operating time varies between 2.5 and 4 h depending on the intra-abdominal conditions following previous surgeries and the type of gastrostomy that is constructed (conventional Stamm tube or a vascularised non-refluxing gastric tube [2]). In view of their often precarious respiratory and physical state, these children benefit from a brief postoperative period of assisted ventilation, physiotherapy and intensive care management. Recovery is usually uneventful and gastrostomy feeds and oral intake commence once bowel function becomes established, commonly within 3–5 days.

Indications

'*Primary OGD with gastrostomy*' should ideally be offered as the single definitive procedure since it meets the family or caregivers' criteria for one safe operation that will eliminate the risk of recurrence of reflux; that will reduce the incidence of aspiration, chest infections and hospitalisation; that will allow better nutrition and growth; and that will improve the quality of life for the child and the family. Primary OGD offers the best prospect of a successful outcome with minimal morbidity. 'First time' surgery offers the surgeon clean unscarred tissues and free natural surgical planes such that dissection is possible with little tissue trauma and bleeding and minimal risk to the lower oesophageal blood supply and to the posterior vagus nerve. Recovery is therefore rapid and the incidence of both short- and long-term complications significantly reduced.

'*Rescue OGD*' is indicated as a salvage procedure following failure of conventional antireflux surgery. Previous intervention/s add to the operative morbidity because of significant adhesions to the liver and to the diaphragm, disruption of the oesophageal hiatus and possible injury to the vagus nerves. It is necessary to unravel the previous fundoplication/s and the attendant scarring and to restore the original anatomy. The condition of the lower oesophagus may be significantly reduced with a poor muscle wall and a reduced blood supply leading to a greater risk of lower oesophageal perforation and breakdown or stricture at the oesophagojejunal anastomosis. It may be necessary to cut back the lower oesophagus to ensure a safe well-vascularised oesophago-jejunal anastomosis. Despite this additional potential morbidity, the long-term benefits far outweigh the risks.

'*Additional indications*' for OGD [3] in otherwise difficult situations are presented in Table 98.1. Experience has shown that OGD can be considered where there has been a need to ensure free oesophageal transit of food to the small bowel and without clinically relevant reflux. It is self-evident that such complex surgery, particularly following on previous operative interventions, carries a greater risk and is best undertaken in a specialist centre well experienced in oesophageal surgery. Potential risks and complications are similar to those associated with rescue OGD; however, once again OGD offers major benefits from effective resolution of the original pathology.

Table 98.1 Additional indications for OGD

Reflux to colon interposition	3
Congenital short oesophagus	1
Congenital lower third oesophageal stenosis	1
Dysfunctional oesophagus following tracheoesophageal cleft	1
Post gas bloat stomach necrosis	1
Bleeding remnant after subtotal gastric resection	1
Microgastria	1

Discussion

The majority of otherwise normal children with significant gastro-oesophageal reflux will respond to conservative medical measures (dietary adjustments, proton pump inhibitors, H_2 receptor antagonists) and will further improve or resolve with growth. For those coming to surgery, a conventional fundoplication remains the recommended first-line management providing effective control of symptoms, low morbidity and a relatively low rate of recurrence of reflux. The mentally impaired child is a different surgical proposition, and the high rate of recurrent post-fundoplication reflux requiring additional surgery in these frail and difficult children stimulates consideration of more effective alternatives. Oesophagogastric dissociation [1] was conceived in 1995 for rescue management following recurrence of reflux after multiple failed fundoplication.

Successful outcomes stimulated consideration of primary OGD as the single definitive effective surgery for the mentally impaired child. We believed there was no obvious logical reason for insisting on an initial conventional fundoplication with a high incidence of reflux recurrence within a relatively short time frame. Analysis of published reports [4, 5] suggests that most morbidity associated with OGD relates to operator technique and to poor lower oesophageal quality following on previous surgery. Thus poor tissue handling with trauma and devascularisation will lead to early lower oesophageal perforation and anastomotic dehiscence or late stenosis at the oesophago-jejunal anastomosis. Bleeding and undrained haematoma predispose to a higher risk of sepsis requiring additional surgery. It is relevant particularly after previous surgeries, always to place the oesophago-jejunal anastomosis without tension to a well-vascularised normal oesophagus, necessarily resecting back damaged and weakened oesophageal tissue.

We have continued to build on our published experience [3, 6, 7] and in our own combined series of primary OGD in 40 children and rescue OGD in 14 children; there has been no mortality relating to the operation and the immediate postoperative recovery has been relatively uneventful. Such mortality as there has been has occurred several months later as a consequence of the original condition. There has been no observed instance of recurrence of reflux and other morbidity, although unwelcome and potentially serious has been limited and manageable. Following Primary OGD one child developed a small bowel adhesion obstruction requiring surgery, and two others had an oesophago-jejunal leak that required corrective surgery. One other presented 18 months after OGD with symptoms suggestive of jejunal loop obstruction and was found to have developed a mid-jejunal stricture, presumably of vascular origin, that required resection and anastomosis. A frail 22-year-old adult in poor physical condition and considered virtually terminal developed a left subdiaphragmatic abscess that resolved with antibiotics and drainage without long-term stenosis. Over subsequent years her physical and mental state showed sustained improvement. In the rescue OGD group who had undergone previous operations, one child developed a small oesophago-jejunal leak noted on contrast study that healed with conservative management.

There have been no long-term metabolic or absorptive problems as a consequence of post-OGD anatomy, and specifically anaemia has not occurred. Oesophageal, jejunal loop or intragastric ulceration and bleeding have not been observed. The jejunal Roux loops retained isoperistalsis, and at 40 cm length offered an effective antireflux mechanism such that there has been no evidence of bilious reflux into the jejunal loop and no instance of stenosis at the oesophago-jejunal anastomosis. However one child presented 18 months after surgery with a late

stricture, presumably of vascular origin, at a point half way down the jejunal loop that required resection and anastomosis. It is relevant that oral intake has only been limited by the child's 'swallowing problem' and the discretion of the families or caregivers.

Similar experiences with neurologically impaired children have been published by others [8], and interestingly variations on the original concept are developing with the publication by Fonkalsrud et al. [9] suggesting reconstruction in the form of an isoperistaltic jejunal segment between the dissociated oesophagus and the pyloro-duodenum. OGD is now also finding application within the surgical management of the mentally impaired adult. The initial report by Hazebroek et al. [10] even concludes with the suggestion of 'early OGD as a primary procedure' when the patient is still in good general health and better respiratory condition.

Ongoing follow-up of our patients, presently at 14 years, confirms the well-documented studies reported by Gatti et al. [11] and Dall'Oglio et al. [12] documenting the marked improvement following OGD, in general well-being, physical growth and lung function, with a striking reduction in aspiration episodes and hospitalisation. Just as significant has been the beneficial impact on the parents and caregivers who invariably attested to the major improvement in quality of life for the child, for themselves and for the family.

The encouraging results from OGD led us to consider other possible indications as detailed in Table 98.1. In these otherwise difficult surgical circumstances [3, 6], we were able to provide free oesophageal transit into the small bowel and without reflux, with the children demonstrating renewed growth and improved quality of life. A similar experience published by Lagausie et al. [13] in 2005 further emphasises the safety and versatility inherent to OGD. Based on this experience, we venture to speculate that OGD may even have a role in the management of the dysfunction associated with the dilated megalo-oesophagus and in achalasia following a failed Heller's procedure.

Review of the published literature [14] to 2008 and our own experience leads us to the conclusion that oesophagogastric dissociation is a reasonably safe procedure that indeed meets the criteria set by the families and caregivers. We have been favourably encouraged by their ongoing appreciation and recommendation of the procedure that has been underpinned by the great improvement in well-being and quality of life for the children and their families. Our positive experience with a young adult supported by the published report from Hazebroek et al. [9] suggests that the same is likely to hold true for adults.

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Gastrostomy Feeding and Gastroesophageal Reflux

99

Peter B. Sullivan

Several clinical conditions require adjunctive tube feeding in order to maintain a normal nutritional state for the patient. Commonly in clinical practice, a nasogastric tube is used for this purpose, but for longer periods of time, or for indefinite use, this method of delivering enteral feeds is less acceptable than gastrostomy tube feeding [13, 43]. For much of the twentieth century, the Stamm gastrostomy, which requires open surgical laparotomy, was the most commonly accepted insertion technique. This was until 1979 when Ponsky and Gauderer introduced the percutaneous endoscopic gastrostomy (PEG) technique [18]. PEG has the advantage that it is minimally invasive, it can be performed by a gastroenterologist, it is relatively inexpensive, and, if the patient's condition precludes use of a general anesthetic, it can be performed under sedation. A PEG may also be placed with laparoscopic assistance when anatomical variants preclude the conventional PEG insertion technique [17].

Indications for Gastrostomy Tube Feeding

The range of indications for insertion of a PEG is extensive (see Table 99.1). The commonest indication for PEG insertion in pediatrics is to overcome oral-motor impairment and feeding difficulties in children with neurological impairment; the largest single group is children with cerebral palsy. Contraindications to gastrostomy tube insertion are listed in Table 99.2.

In children with neurological impairment gastrostomy, placement has been shown to significantly increase weight, reduce feeding time, and reduce both feed-related choking episodes and frequency of chest infections [27, 54, 57]. Family stress is significantly reduced [27], and quality of life of parents increases after PEG insertion to assist feeding [58]. Severe oral-motor dysfunction is a marker for the severity of degree of neurological dysfunction. Accordingly, children with severe neurological impairment who require gastrostomy feeding have a substantial long-term mortality. This is probably related more to the underlying neurological condition than it is to PEG placement [9].

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Table 99.1 Indications for insertion of a gastrostomy feeding tube

Failure of adequate nutritional intake
Oral-motor dysfunction (>50 % the commonest indication)
Craniofacial abnormalities
Head and neck trauma
Supplemental alimentation in those with increased calorie requirements
Malignancy and chemotherapy
Chronic renal failure
Cystic fibrosis
Congenital heart disease
Crohn's disease
Short bowel syndrome
Human immunodeficiency viral infection
Prolonged dependence on nasogastric tube feeding (>6 weeks)
Unsafe airway
Recurrent aspiration
Gastric drainage/decompression
Motility disorders
Short-bowel syndrome

Table 99.2 Contraindications to insertion of a gastrostomy feeding tube

Sick, unstable patient, e.g., in heart failure
Coagulopathy/bleeding disorders
Peritonitis
Severe ascites
Gastric varices
Distorted anatomy
E.g., 2° to severe kyphoscoliosis
Colonic interposition
Oesophageal obstruction
Hepatosplenomegaly
Failed diaphanoscopy

Complications of Gastrostomy Tube Feeding

Insertion of a PEG feeding tube carries with it a relatively low risk of complications. The result from Larson's series, which includes both adults and children, is typical of the published literature and revealed a procedure-related mortality of 1 %, a major complication rate of 3 %, and a minor complication rate of 13 % [35]. The commonest minor complication is infection of the gastrostomy insertion site and overgrowth of granulation tissue. Major complications are rare and include wound infection, cellulitis, oesophageal injury (probably sustained during extraction of the guide wire), abdominal wall abscesses, necrotizing fasciitis, gastrocolic fistula, colocutaneous fistula, duodenal hematoma, complicated pneumoperitoneum, gastric perforation, peritonitis, acute gastric dilatation, and gastroduodenal obstruction caused by the balloon of the gastrostomy catheter. Those patients with multisystem organ failure have an increased rate of complications and a poor response to nutritional support; for this population, the risk of PEG may outweigh its benefit [38].

Many of these complications can be avoided or reduced in likelihood by refinements to the technique of insertion [3]. A further complication and one which produces significant issues in relation to clinical management is symptomatic gastroesophageal reflux (GER) occurring after PEG insertion [27, 56].

Gastroesophageal Reflux

Gastroesophageal reflux (GER) is common in children with cerebral palsy, the largest group in whom a gastrostomy feeding tube is inserted, and occurs in 19–75 % of such cases [21, 48, 53, 59]. Central nervous system dysfunction is the prime cause of this high incidence of GER in children with cerebral palsy. Additional contributory factors include hiatus hernia, adoption of a prolonged supine position, and increased intra-abdominal pressure secondary to spasticity, scoliosis, or seizures [22, 24]. As a result of neuromuscular incoordination in the foregut, the anti-reflux function of the lower esophageal sphincter mechanism and esophageal motility are significantly impaired. Gastric dysmotility and delayed gastric emptying may also predispose toward GER in children with neurological impairment [2, 4, 8, 42], although

this relationship has not been demonstrated in all studies [6, 30, 41, 52].

Insertion of a Stamm gastrostomy has been shown to reduce lower esophageal sphincter (LES) pressure and predispose to GER [7, 32]. Studies following PEG insertion have shown both an increase in LOS pressure [29], and no effect on basal LES pressure unless rapid bolus feeds are delivered via the tube [10].

Similarly, some authors have found no relationship between PEG insertion and GER [37, 47, 49, 56], whereas others have [20, 27]. The reported postoperative prevalence of GER as a complication of PEG insertion varies from 13 % to 28 % [26, 28, 33, 56]. It may be that the site of insertion of the gastrostomy tube has an influence on the development of postoperative GER, and some endoscopists have found that tube placement in the antrum or lesser curve is associated with less subsequent reflux [47, 50].

Given the uncertainty about whether PEG insertion will exacerbate GER in the individual patient, especially those with foregut dysmotility, it would seem prudent to establish whether or not GER exists preoperatively [19]. Unfortunately, no test has been shown reliably to predict which patients will develop clinically significant GER post-PEG insertion. Despite normal clinical history and preoperative radiological and lower esophageal pH studies, GER can become apparent in neurologically impaired children after gastrostomy tube placement [5]. Much of the evidence in the literature is conflicting as a result of relatively small studies in selected cases, but the larger studies have shown no significant difference in GER symptoms or median reflux index on 24-h lower esophageal pH monitoring before and after PEG insertion [33, 37, 47]. Even preoperative histological evidence of esophagitis is poorly predictive of subsequent significant GER [12, 26]. In practice a pragmatic attitude should be adopted which takes into account the extent of clinical symptoms of GER (vomiting, aspiration, etc.) prior to PEG insertion and then selects those patients with significant clinical symptoms for investigation by prolonged lower esophageal pH monitoring and barium or water-soluble contrast studies to determine the need for a surgical anti-reflux procedure or jejunostomy [19].

Surgical Anti-reflux Procedures

The notion of a "prophylactic" anti-reflux procedure following gastrostomy insertion especially in children with neurological impairment was advocated by some [31]. The consensus' view now, however, is that such an approach is not advisable [14, 23, 33, 34, 45, 51, 56, 61, 62]. A major reason for this view is that fundoplication is associated with a higher morbidity and mortality rates in neurologically impaired children, when compared with neurologically normal children [36, 40, 44, 46].

Postoperative morbidity rates of up to 50 % and reoperation rates of up to 20 % and mortality rates up to 50 % are quoted following standard Nissen fundoplication [1, 40]. Major complications can occur both intra- and postoperatively including hepatic vein laceration, bowel perforation, tension pneumothorax, paraesophageal hernia, and small bowel obstruction [44]. Children with neurological impairment have more than twice the complication rate, three times the morbidity rate, and four times the anti-reflux reoperation rate than non-neurologically impaired children [15, 44]. In one study, for instance, more than 30 % of children with neurological impairment had major complications or died within 30 days of surgery, and 25 % had documented operative failure [39]. In another report, nearly one half of neurologically impaired children had documented recurrent GER after surgery [40]. Recurrent GER often leads to a second operation, but these repeats have a failure rate of around 30 % [11, 55, 60].

No single symptom is reliably predictive of recurrent GER so it is necessary to have a high index of suspicion for the development of recurrent GER after anti-reflux procedure in neurologically impaired children and to have a low threshold for proceeding to upper GI contrast study and lower esophageal pH study or endoscopy to investigate this possibility [39].

Medical Management of Gastroesophageal Reflux

The advent of proton-pump inhibitors (PPI) for use in children has had a very significant impact on the treatment of GER. Just as increasing experience of the complications following fundoplication has been shown to raise the threshold for performing this operation in children with neurological impairment [51] so has the efficacy of PPI as medical treatment been associated with a dramatic decrease in the number of surgical antireflux procedures performed in children [25].

In conjunction with PPI therapy, strategies to control reflux include a change from bolus to continuous pump feeding [10] and use of whey-predominant enteral milk formulae which have been shown to be associated with faster gastric emptying and less reflux [16].

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Part XVII

Evaluation and Management of the Pediatric Patient with Suspected GERD

Regurgitation in Infants

100

O. Kirmemis

Gastroesophageal reflux (GER) is defined as the involuntary passage of gastric contents from the stomach into the esophagus. *GER disease* (GERD) on the other hand is a condition that develops if GER causes troublesome symptoms and/or complications such as pain, poor growth, and esophagitis [1]. *Regurgitation* is defined as the effortless return of stomach contents into the mouth. *Vomiting* is a coordinated reflex and is defined as expulsion of the refluxed gastric contents from the mouth (Fig. 100.1). However, the difference between regurgitation and vomiting is not always clearcut [1–3].

Regurgitation is a common problem in infancy, affecting about 50 % of all babies at the age of 2 months [1]. Most of the infants do not experience long-term symptoms; however, symptoms can result in significant parental anxiety and infant discomfort [2]. Most reflux episodes are asymptomatic, brief, and limited to the distal esophagus. "Excessive regurgitation" is one of the symptoms of GERD, but the terms regurgitation and GERD should not be used as synonyms.

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About 70 % of healthy infants have regurgitation that is physiologic, resolving without intervention in about 95 %, by the age of 12–14 months [4] (Fig. 100.2). Daily regurgitation occurs more frequently in infants during the first 6 months of life than in older infants and children. Frequent regurgitation, defined as more than three times per day, occurs in about 25 % of infants during the first months of life.

Various studies report a comparable incidence of regurgitation in unselected populations of formula versus breast-fed infants. Exclusively breastfed infants regurgitate less than partially breastfed babies [5]. This observation fits with the knowledge that GER and symptoms of GER (GERD) may be indistinguishable from those of food allergy [6]. Moreover, the association between GERD and cow milk hypersensitivity was observed in both infants and children with severe GERD [7, 8].

The Infant with Uncomplicated Regurgitation

Uncomplicated regurgitation in otherwise healthy infants is not a disease. Common causes include overfeeding and air swallowed during feeding, crying, or coughing. The typical presentation of uncomplicated infant GER is an effortless, painless regurgitation in a healthy-appearing child with normal growth, the so-called happy spitter.

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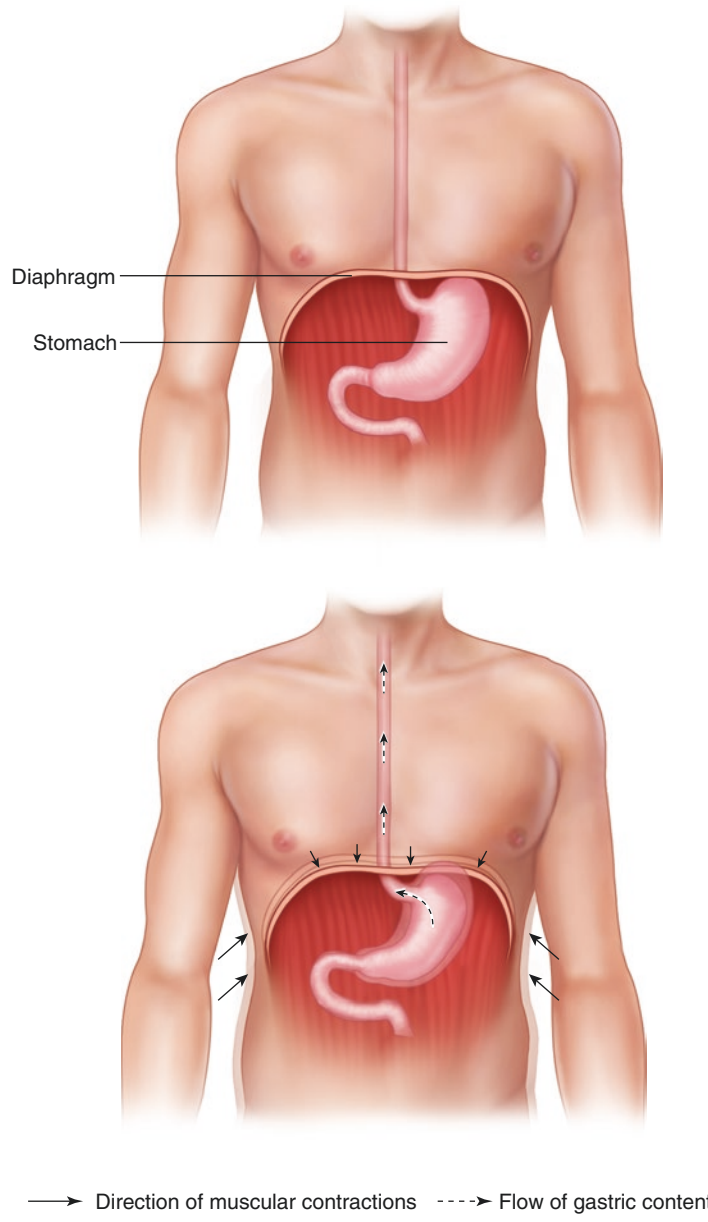
Fig. 100.1 Mechanism of vomiting



Intermittently, an episode of vomiting, even forceful vomiting may occur. Irritability may accompany regurgitation and vomiting; however, in the absence of other warning symptoms, it is not an indication for extensive diagnostic testing. Recurrent regurgitation generally decreases over the first year and disappears about 18 months of age [9]. If there are "warning signs" suggestive of GERD or other pathologic underlying diseases, consultation with a pediatric gastroenterologist is recommended. The same approach is to consider if symptoms persist over the age of 18 months [3].

Uncomplicated regurgitation is a benign condition with a good prognosis, needing no other intervention than parental education and anticipatory guidance (Fig. 100.3). Modification of

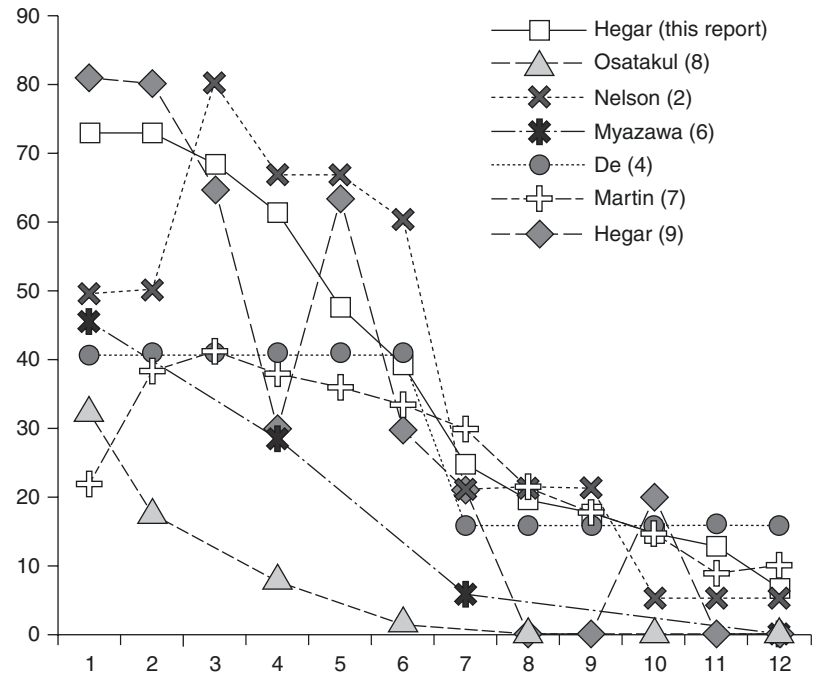


Fig. 100.2 Natural evolution of physiologic regurgitation (Data from Hegar et al. [5])

milk composition (adition of thickening agents), feeding frequency, volume, and sleep position may be indicated [10, 11]. Overfeeding exacerbates recurrent regurgitation.

Thickening of feeding formula has been demonstrated to reduce almost consistently the frequency and volume of regurgitation and result in an increased caloric intake [12–14]. Use of a thickened formula (or commercial anti-regurgitation formulae, if available) may decrease visible regurgitation but does not result in a measurable decrease in the frequency of esophageal reflux episodes.

Prone positioning decreases the amount of acid esophageal exposure measured by pH probe compared with that measured in the supine position. However, prone and lateral positions are associated with an increased incidence of sudden infant death syndrome (SIDS). The risk of SIDS outweighs the benefit of prone or lateral sleep position on GER; therefore, in most infants from birth to 12 months of age, supine positioning during sleep is recommended [3].

There is no evidence that antisecretory or promotility agents improve physiologic infant regurgitation [3].

In infants with persistent uncomplicated regurgitation and no respond to previous management, a 2–4-week trial of protein hydrolysate- or amino acid-based formula or a trial of milk-free diet for the breast-feeding mother is appropriate in order to exclude cow's milk allergy [3, 7, 8].

Regurtitation and Irritability

Reflux is an uncommon cause of irritability or unexplained crying in otherwise healthy infants. However, if irritability persists with no explanation other than suspected GERD, expert opinion suggests the following options. The practitioner may continue anticipatory guidance and training of parents in the management

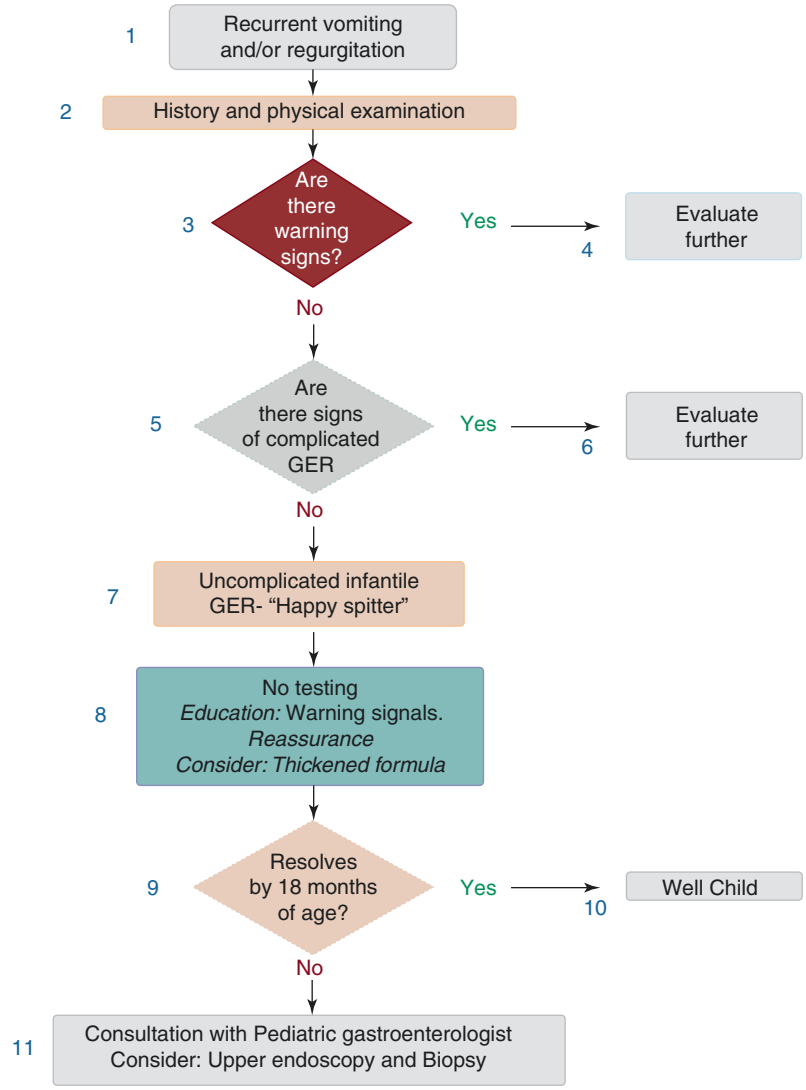


Fig. 100.3 Approach to the infant with uncomplicated recurrent regurgitation (happy spitter) [10]

of such infants with the expectation of improvement with time. Additional investigations to ascertain the relation between reflux episodes and symptoms or to diagnose reflux or other causes of esophagitis may be indicated (pH monitoring, impedance monitoring, endoscopy). A time-limited (2-week) trial of antisecretory therapy may be considered, but there is potential risk of adverse effects and clinical improvement following empiric therapy maybe due to spontaneous symptom resolution or a placebo response. The risk/benefit ratio of these approaches is not clear [3].

The Infant with Recurrent Regurgitation Poor Weight Gain

Poor weight gain is a crucial warning sign that necessitates clinical management. These infants need a complete diagnostic workup, starting with a dietary history to evaluate caloric intake. A feeding history should be obtained that includes an estimate of energy offered and ingested per day, an estimate of energy loss through regurgitation, a description of formula preparation and feeding schedule, an assessment

Table 100.1 Differential diagnosis of vomiting in infants and children

Gastrointestinal obstruction
Pyloric stenosis
Malrotation with intermittent volvulus
Intestinal duplication
Hirschsprung disease
Antral/duodenal web
Foreign body
Incarcerated hernia
Other gastrointestinal disorders
Achalasia
Gastroparesis
Gastroenteritis
Peptic ulcer
Eosinophilic esophagitis/gastroenteritis
Food allergy
Inflammatory bowel disease
Pancreatitis
Appendicitis
Neurologic
Hydrocephalus
Subdural hematoma
Intracranial hemorrhage
Intracranial mass
Infant migraine
Chiari malformation
Infectious
Sepsis
Meningitis
Urinary tract infection
Pneumonia
Otitis media
Hepatitis
Metabolic/endocrine
Galactosemia
Hereditary fructose intolerance
Urea cycle defects
Amino and organic acidemias
Congenital adrenal hyperplasia
Renal
Obstructive uropathy
Renal insufficiency
Toxic
Lead
Iron
Vitamins A and D
Medications—ipecac, digoxin, theophylline, etc.
Cardiac
Congestive heart failure
Vascular ring
Others
Pediatric falsification disorder (Munchausen syndrome by proxy)
Child neglect or abuse
Self-induced vomiting
Cyclic vomiting syndrome
Autonomic dysfunction

of breast milk sufficiency, and a description of infant sucking and swallowing behavior. Parents should be advised not to reduce intake to the point of energy deprivation in the attempt to prevent regurgitation. If problems identified by history seem to explain the symptoms and can be addressed, close outpatient monitoring of weight gain will determine whether further evaluation is indicated [3].

If chronic regurgitation and inadequate weight gain persist after observation and despite adequate energy intake, once other causes of vomiting have been ruled out. Infections (especially urinary tract), anatomic abnormalities, neurologic disorders, food allergy, and metabolic disease are among possible etiologies of

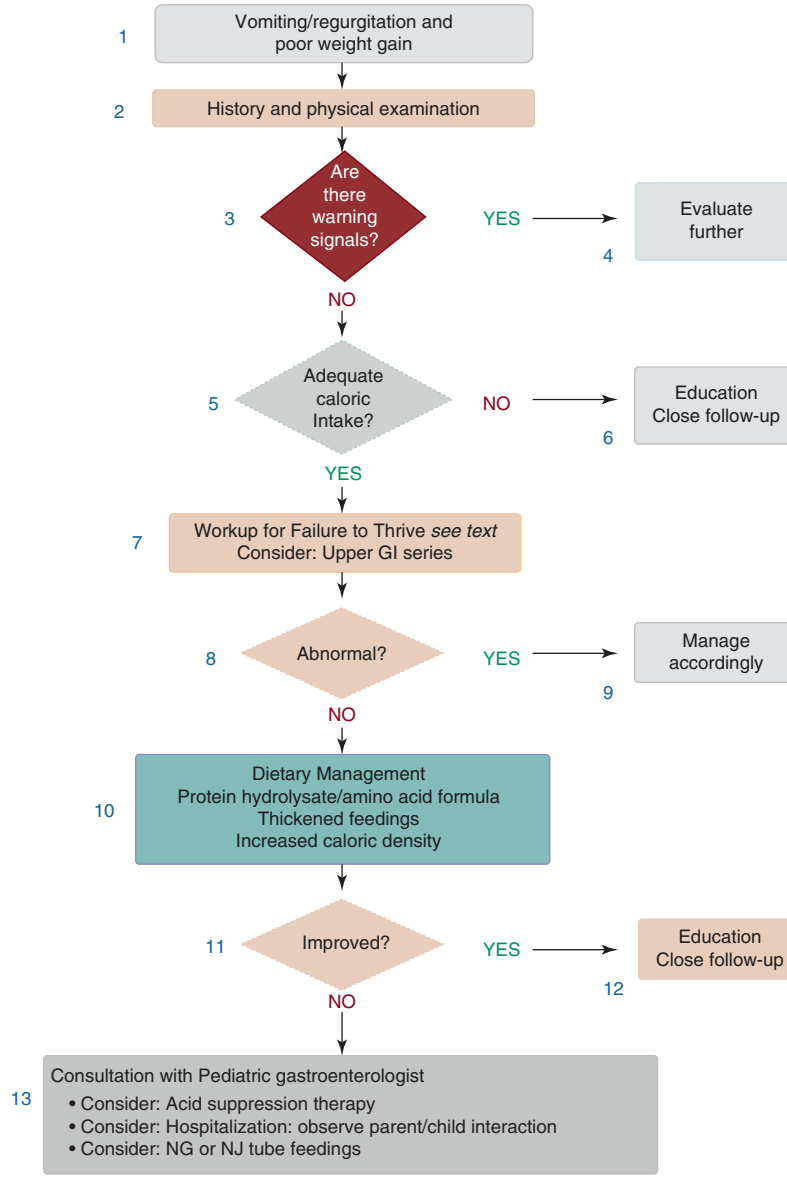


Fig. 100.4 Approach to the infant with recurrent regurgitation and poor weight gain

regurgitation and poor weight gain in infancy (Table 100.1).

A 2–4-week trial of extensively hydrolyzed or amino-acid-based formula is appropriate. Thickening the formula is recommended since it has been shown to help both irritability and weight gain. Depending on the results of investigations and response to dietary management, the infant should be referred to a pediatric specialist (Fig. 100.4). Hospitalization for observation and testing is appropriate in some infants with persistent failure to thrive. Therapy with H2 receptor antagonists and proton pump inhibitors may be suggested in cases with confirmed GERD [11]. Nasogastric or nasojejunal feeding is occasionally necessary to achieve weight gain in the infant with no other clear explanation for poor weight gain [15].

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Recurrent Regurgitation and Vomiting in Children

101

Prithviraj Rao and Mike Thomson

Abbreviations

CNS	Central nervous system
CTZ	Chemoreceptor trigger zone
GORD	Gastro-oesophageal reflux disease

Definition

Vomiting is the forceful expulsion of the contents of one's stomach through the mouth and sometimes the nose. Regurgitation (or gastro-oesophageal reflux) differs from vomiting in that it is an involuntary and effortless expulsion of undigested gastric content back up the oesophagus to the mouth, without the force and displeasure associated with vomiting. It's however difficult to make a distinction between the two mechanisms in infants and young children.

Pathophysiology

There may be either or both mechanisms contributing to the symptom of vomiting:

1. The emetic reflex (see Fig. 101.1) [1]
2. The incompetence of the anti-reflux barrier

The emetic reflex is coordinated in an area within the CNS called the 'vomiting centre' where all the afferent stimuli are processed and integrated. The vomiting centre includes the reticular formation of the brain stem, supraoptic and paraventricular nuclei of the hypothalamus and receptors on the floor of the fourth ventricle of the brain known as the area postrema (or CTZ), stimulation of which can lead to vomiting. In a more simplistic way, the process can be divided into 'input' and 'output'.

Input

The various sources of input to the vomiting centre are:

- Vagus nerve, which is activated when the pharynx is irritated, leading to a gag reflex for, e.g. in pharyngitis.
- Vagal and enteric nervous system transmit information regarding the state of the gastrointestinal system. Irritation of the GI mucosa

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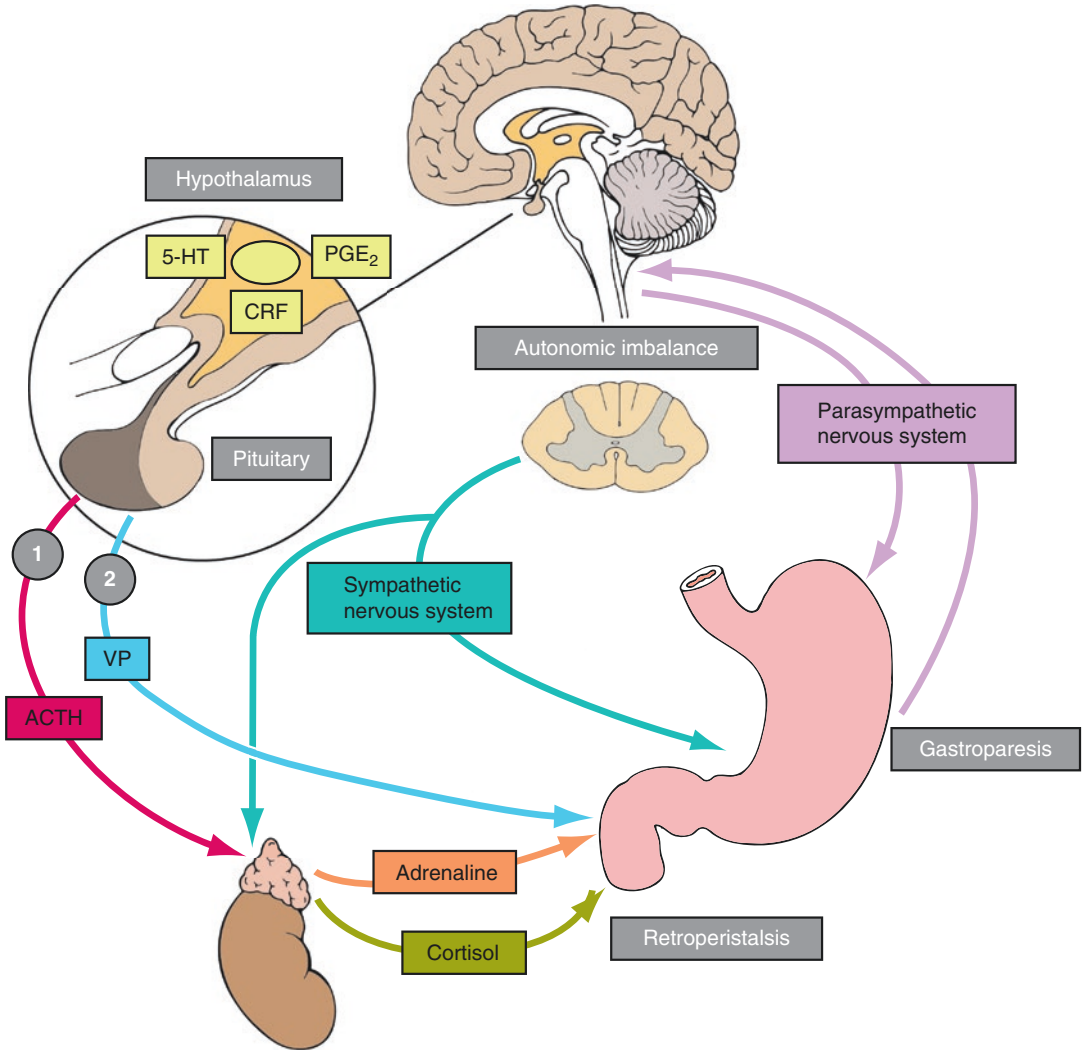

Fig. 101.1 The emetic reflex

by acute infectious gastroenteritis, chemotherapy, radiation or distention activates the 5-HT_3 receptors of these inputs.

- The vestibular system which sends information to the brain via vestibulocochlear nerve. It plays a major role in motion sickness and is rich in muscarinic and histamine H_1 receptors.
- The CNS mediates vomiting arising from psychiatric disorders and stress from higher brain centres, namely, cerebral cortex and limbic system [2].
- The CTZ has serotonin 5-HT_3 receptors, opioid receptors, acetylcholine receptors, dopamine D_2 receptors and receptors for substance P. Stimulation of different receptors is involved in different pathways leading to emesis [3].

Output

The vomiting act encompasses three types of outputs initiated by the chemoreceptor trigger zone: motor, parasympathetic nervous system (PNS)

and sympathetic nervous system (SNS). They are as follows:

Motor output—results in lowering of intrathoracic pressure (by inspiration against a closed glottis) coupled with contraction of the diaphragm, anterior abdominal wall and intercostal muscle, thus propelling stomach contents into the oesophagus. Vomiting is ordinarily preceded by retching.

PNS output—increased salivation to protect the enamel of teeth from stomach acids (excessive vomiting leads to dental erosion).

A deep breath is taken to avoid aspiration of vomit.

Retroperistalsis, starting from the middle of the small intestine, sweeping up the contents of the digestive tract into the stomach, through the relaxed pyloric sphincter.

SNS output—causes both sweating and increased heart rate.

The neurotransmitters that regulate vomiting are poorly understood, but inhibitors of dopamine, histamine and serotonin are all used to suppress vomiting, suggesting that these play a role in the initiation or maintenance of a vomiting cycle. Vasopressin and neurokinin may also participate. The area postrema as such lies outside the blood-brain barrier and can therefore be stimulated by humoral stimuli, cytotoxins, ketones, ammonia and blood-borne drugs that can stimulate vomiting or inhibit it.

Aetiology

The causes of vomiting are listed in the table below with the majority of the organic causes being digestive (gastrointestinal, pancreatic or hepatobiliary) (Table 101.1).

Types of Vomiting

Vomit of Food It's the most frequent type of vomiting and is more often due to primary or secondary GOR. It is thus made of partially digested or undigested food and may occur immediately after a meal or after a few hours.

In an infant with recurrent regurgitation, a thorough history and physical examination with attention to warning signals suggesting other diagnoses (Table 101.2) is generally sufficient to establish a clinical diagnosis.

In infants with uncomplicated GOR, there is no need for extensive diagnostic testing if they demonstrate normal growth and in the absence of other warning symptoms. Recurrent regurgitation due to GOR generally decreases over the first year, resolving at 12–18 months of age [4, 5]. Only parental education, anticipatory guidance and modification of feeding frequency and volume are necessary for the management uncomplicated infant GOR [6, 7]. Overfeeding exacerbates recurrent regurgitation and should be avoided [8]. In some infants with persistent regurgitation, a thickened or commercial anti-regurgitation formula may help control the frequency of regurgitation. Since regurgitation is sometimes the sole manifestation of cow's milk protein allergy in healthy-looking infants, a 2-week trial of protein hydrolysate or amino acid-based formula or a trial of milk-free diet for the breast feeding mother is appropriate. If warning signals are present, further evaluation will be necessary.

The commonest causes of food vomitus in an older child are GOR and cyclical vomiting syndrome which is described later:

'Acid' Vomits The vomitus tends to be mucousy or foamy with a pH of <5.

In infants, it's usually associated with crying and irritability which are nonspecific symptoms associated with a wide range of physiologic and pathologic conditions. Some normal healthy infants cry as much as six hours per day. Likewise there is variation in parental perceptions regarding the severity and duration of crying and its importance. Top on the list of differential diagnosis for pathologic conditions would be GOR.

Table 101.1 Differential diagnosis of vomiting in infants and children

Gastrointestinal obstruction	*Metabolic/endocrine*
Pyloric stenosis	Galactosemia
Malrotation with intermittent volvulus	Hereditary fructose intolerance
Intestinal duplication	Urea cycle defects
Intestinal pseudo-obstruction	Amino and organic acidemias
Hirschsprung disease	Congenital adrenal hyperplasia
Antral/duodenal web	Addison disease
Foreign body	Diabetic ketoacidosis
Incarcerated hernia	Pheochromocytoma
Superior mesenteric artery syndrome	Disorders of fatty acid oxidation
Other gastrointestinal disorders	Mitochondriopathy
Gastro-oesophageal reflux disease (peptic oesophagitis)	Acute intermittent porphyria
Peptic disorders (gastritis, duodenitis, Helicobacter pylori infection)	*Renal*
	Obstructive uropathy
Achalasia	Renal insufficiency
Gastroparesis	Acute hydronephrosis secondary to
Gastroenteritis	Uretero-pelvic junction obstruction
Peptic ulcer	Nephrolithiasis
Eosinophilic oesophagitis/gastroenteritis	*Toxic*
Food allergy	Lead
Inflammatory bowel disease	Iron
Pancreatitis	Vitamin A and D
Hirschsprung disease	Medications
Cholelithiasis (gallbladder dyskinesia)	*Cardiac*
Choledochal cyst	Congestive heart failure
Chronic appendicitis	Vascular ring
Neurologic	*Psychiatric*
Hydrocephalus	Munchausen syndrome by proxy
Subdural hematoma	Bulimia
Intracranial haemorrhage	Self-induced vomiting
Intracranial mass	*Social*
Migraine	Child neglect
Infectious	Child abuse
Chronic sinusitis	*Others*
Sepsis	Familial dysautonomia (Riley-Day syndrome)
Meningitis	Pregnancy
Urinary tract infection	
Pneumonia	
Otitis media	
Hepatitis	

Incorporated from NASPGHAN–ESPGHAN guidelines

Vomiting associated with GOR is probably a result of the stimulation of pharyngeal sensory afferents by refluxed gastric contents.

The available evidence does not support an empiric trial of acid suppression in infants with irritability or sleep disturbance [5]. A symptom diary [6, 7] or hospital observation [8, 9] may be useful to confirm the history, which is very subject to observation bias. Disorders other than GORD to consider include cow's milk protein allergy [10] and causes as listed in Table 101.1. Allergy to cow's milk protein or other formula intolerance may cause infant irritability, distress and vomiting indistinguishable from GORD. An empiric trial of extensively hydrolyzed protein formula or amino-acid-based formula is reasonable in selected cases.

GORD may present as epigastric pain, heartburn or dysphagia in children and a systematic approach is necessary.

Bilious Vomits Always an ominous sign particularly in infants and suggestive of intestinal obstruction distal to the ampulla of Vater. In

Table 101.2 Warning signals requiring investigation in infants with regurgitation or vomiting

Projectile vomiting
Bilious vomiting
GI bleeding
Haematemesis
Haematochezia
Consistently forceful vomiting
Onset of vomiting after 6 months of life
Failure to thrive
Diarrhoea
Constipation
Fever
Lethargy
Hepatosplenomegaly
Bulging fontanelle
Macro-/microcephaly
Seizures
Abdominal tenderness or distension
Documented or suspected genetic/metabolic syndrome
Associated chronic disease

older children is possibly due to persistent stimulation of the emetic reflex. Diagnostic clue would be within the history of initial expulsion of gastric contents or mucus only, followed by expulsion of bile on subsequent episodes.

Bloody Vomits (Haematemesis) Are a potential emergency and needs evaluation in the hospital setting. Vomits containing bright red blood or coffee-ground material are suggestive of ongoing or recent bleeding from the upper GI tract. Haematemesis is usually a complication of an underlying disease such as peptic disease, coagulopathy, oesophageal varices, etc. A thorough history and examination including an ear, nose and throat assessment is necessary.

Investigations: Barium upper GI series, upper gastrointestinal endoscopy and oesophageal pH/MII both to diagnose GERD and rule out alternative diagnoses.

Cyclical Vomits This condition is described in greater detail in the next section of this chapter.

Cyclical Vomiting Syndrome

Introduction

Cyclic vomiting syndrome (CVS) is an episodic disorder of nausea and vomiting that was first described by Dr. W. Heberden in the French literature in 1806 [11] and then by Dr. Samuel Gee [12] in the English literature in 1882. The syndrome is a functional disorder considered to be a manifestation of migraine diathesis [13, 14] with a characteristic pattern of recurrent episodes of high-intensity nausea and vomiting lasting hours or days, separated by intervals free of symptoms. The pattern has many aetiologies. Patients typically present with six to twelve stereotypic episodes of nausea and vomiting per year that vary in duration and frequently go undiagnosed for years [15]. The diagnosis is primarily based on history and clinical presentation. Treatment focuses on symptom management and prompt measures aimed at aborting or terminating episodes. Anti-migraine medications have been effectively used for prophylaxis in many patients.

Diagnostic Criteria

As per the consensus statement by the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) [16] (Table 101.3).

Epidemiology

CVS has been described in all races and ethnicities, although Caucasians appear to be effected to a greater degree. The prevalence of CVS is not known and appears to vary depending on geographical location. In a population-based study performed in Aberdeen, Scotland [17] indicated a prevalence of 1.9 % (though this is likely to be an overestimate), whereas Li and Misiewicz [18] estimated it to be 0.04 % in children of central Ohio. Affected children are more often girls than boys (60:40) of elementary school age (ranging from infants to young adults).

Table 101.3 Diagnostic criteria for cyclical vomiting syndrome

At least 5 attacks in any interval or a minimum of 3 attacks during a 6-month period
Episodic attacks of intense nausea and vomiting lasting 1 h–10 days and occurring at least 1 week apart
Stereotypical pattern and symptoms in the individual patient
Vomiting during attacks occurs at least 4 times/h for at least 1 h
Return to baseline health between episodes
Not attributed to another disorder

CVS occurs in all age groups. Children as young as 6 months and adults as old as 73 years have been described as having CVS. The median age at onset of symptoms ranges from 5.2 to 6.9 years.

Symptoms and Associated Features

CVS usually has four different phases: prodromal, vomiting, recovery and inter-episodic. Understanding of this phasic pattern helps in both diagnosis and management. The inter-episodic phase is more or less symptom-free. The patient senses the approach of an episode during the prodromal phase, but is still able to retain oral medications. The vomiting phase is characterized by intense, persistent nausea, vomiting, retching and other symptoms. The recovery phase begins as soon as nausea remits and ends when the patient has recovered appetite, strength and body weight lost during the vomiting phase.

Grading of severity	
Mild	CVS not interfering with work or school
Moderate	If attendance at work or school in jeopardy
Severe	If disabled

Prodromal symptoms consist of nausea, lethargy, anorexia and pallor. A migraine-like visual aura is rare. The nausea, vomiting, retching and other symptoms of the vomiting phase are overwhelming and completely incapacitating. Their mean duration is 41 h (median, 24 h). The maximum frequency of vomiting may be more than ten times per hour. Forceful vomiting and retching often cause haematemesis due to prolapse gastropathy or Mallory-Weiss tears [19–21]. Peptic oesophagitis and haemorrhagic lesions of the gastric mucosa are typical endoscopic findings that result from, rather than cause, vomiting episodes. Signs and symptoms of an intense stress response are common, including increased heart rate and blood pressure, drenching diaphoresis, minor loose stooling, low-grade fever and neutrophilia. Many children have behaviours during episodes that may puzzle or mislead carers, but remit promptly during the recovery phase. Headache (40 %), photophobia (32 %) and phonophobia (28 %) may occur and cause patients to seek a quiet and dark environment.

Diagnostic Approach

There are no specific laboratory markers to diagnose CVS. A pattern of recurrent, episodic vomiting in children that fulfils the revised historical criteria listed in Table 101.3 is likely (about 90 %) to be ultimately diagnosed as idiopathic CVS [20]. The challenge would be to differentiate individuals with specific and serious underlying causes of vomiting (about 10 %) for which prompt treatment may alter outcomes (see Fig. 101.2).

A thorough history and physical examination at presentation helps identify those children in whom further diagnostic testing is prudent. The diagnostic principles outlined below are intended to help identify those children with a cyclic vomiting pattern between ages 2 and 18 years at the greatest risk for having an organic cause.

Suspicious symptoms and physical findings include the following:
1. Bilious vomiting, abdominal tenderness and/or severe abdominal pain
2. Attacks precipitated by intercurrent illness, fasting and/or high protein meal
3. Abnormalities on neurological examination including severe alteration of mental status, abnormal eye movements, papilloedema, motor asymmetry and/or gait abnormality (ataxia)
4. Progressively worsening episodes or conversion to a continuous or chronic pattern

Depending upon the presenting symptoms and signs other than vomiting, different diagnostic approaches are recommended as illustrated in Fig. 101.2.

Although children younger than 2 years may have CVS, serious underlying metabolic and surgical disorders are more frequent and more difficult to diagnose in that age range.

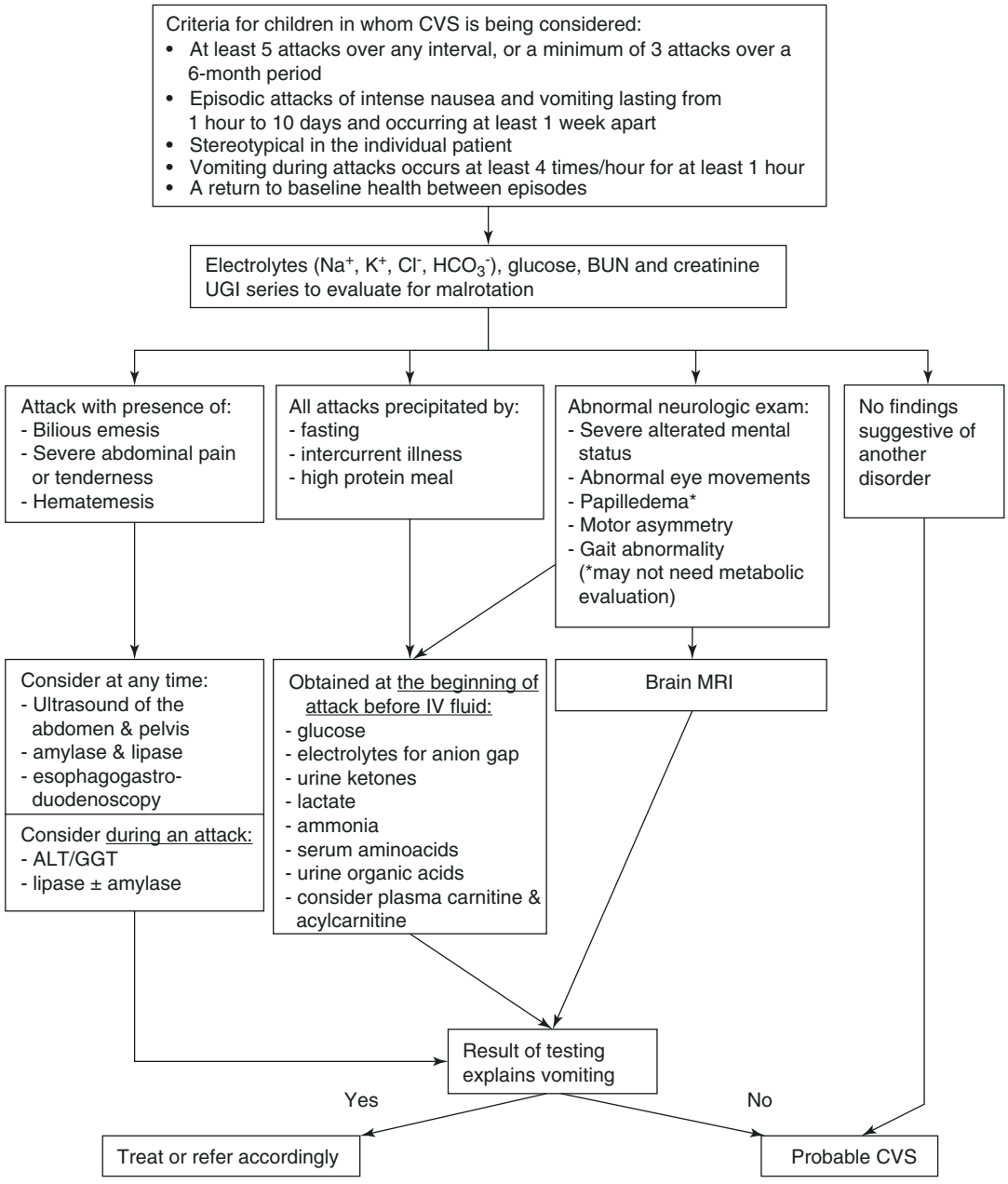

Fig. 101.2 Recommended investigative protocol in children >2 years with cyclical vomiting (Courtesy NASPGHAN: Incorporated from the NASPGHAN consensus statement [16] on CVS)

Children with cyclic vomiting should be evaluated for a possible metabolic or neurological disorder if any of the following conditions are met:

- Presentation under age 2 years (with cyclic vomiting or comorbidities below)
- Vomiting episodes associated with intercurrent illnesses, prior fasting, increased protein intake
- Any neurological finding: ataxia, dystonia or another gait disturbance; mental retardation; seizure
- Disorder or acute encephalopathy (including true lethargy, severe irritability, confusion, psychosis or rapidly changing/unstable mental status)
- Laboratory metabolic findings: hypoglycaemia, substantial anion gap metabolic acidosis, respiratory alkalosis or hyperammonaemia

A referral to a specialist in metabolic disorders and/or a neurologist is suggested for patients with any of the above findings.

Treatment Approach to Recurrent, Episodic Vomiting

The management of CVS requires an individually tailored regimen that takes into consideration the clinical course, frequency and severity of attacks, and resultant disability balanced against the potential side effects of treatment. The clinical course of CVS can be divided into the episode phase and the well phase.

Well Phase During the well phase, lifestyle changes as detailed in Table 101.4 may help reduce episode frequency/intensity.

Because fear and anticipation of future episodes can trigger episodes of CVS, the use of reassurance and anticipatory guidance may help reduce the frequency of attacks. This guidance includes confirming that the attacks are not self-induced and the child will typically improve with age and providing an individualized management protocol.

Table 101.4 Practical therapeutic approach to CVS

Avoid: triggers (vomiting diary to identify potential precipitating factors)
Fasting
Triggering foods (antigenic foods, monosodium glutamate, chocolate, cheese)
Excess energy output (over exercising)
Skipping meals
Sleep deprivation
Provide: fruit juices, other sugar containing drinks
Extra snacks between meals, before exertion or at bedtime
Supplemental carbohydrate for fasting-induced symptoms
Migraine headache life style interventions
Regular aerobic exercise, meal schedules and good sleep hygiene
Recognize that excitement could also be a trigger
Reassurance

Episodic Phase The two key treatment arms are prophylactic (or preventive) measures and medication administered between attacks and acute and supportive interventions given during attacks.

Preventive medications are only indicated if episodes occur frequently (e.g. more than every 1–2 months), are severe enough to cause repeated hospitalisation/school absence and/or fail to respond to abortive therapies.

Recommendations for Prophylaxis

Pizotifen, propranolol or cyproheptadine is the recommended prophylaxis for children 5 years old and younger. In the older child (older than 5 years), pizotifen, amitriptyline or propranolol is recommended, as shown in Table 101.5. The dose can be titrated to effect by increasing it

Table 101.5 Prophylactic or preventive medication in CVS

Children 5 years or younger	
Pizotifen 0.5 mg–1.5 mg/kg/day [first choice]	Side effects: increased appetite, weight gain, sedation
Propranolol 0.25–1.0 mg/kg/day, most often 10 mg bid or tid (second choice). Monitor: resting heart rate maintain 60 bpm	Side effects: lethargy, reduced exercise intolerance
	Contraindications: asthma, diabetes, heart disease, depression
	Discontinuation: tapered for 1–2 weeks
Alternatives	
Cyproheptadine 0.25–0.5 mg/kg/day divided bid or tid b-Blockers:	Side effects: increased appetite, weight gain, sedation
Children older than 5 years	
Tricyclic antidepressants: amitriptyline (first choice)	Side effects: constipation, sedation, arrhythmia, behavioural
Amitriptyline begin at 0.25–0.5 mg/kg qds, increase weekly by 5–10 mg, until 1.0–1.5 mg/kg	
Monitor: (ECG) QTc interval before starting and 10 days after peak dose changes (especially in younger children)	Alternatives: nortriptyline (available in liquid)
b-Blockers: propranolol (second choice)—see above	
Other agents	
Anticonvulsants:	Side effects: sedation, cognitive impairment
Phenobarbital 2 mg/kg qds	Alternatives: topiramate, valproic acid, gabapentin, levetiracetam—consult neurologist
Supplements	
L-carnitine 50–100 mg/kg/day divided bid or tid (max 1 g)	Side effects: diarrhoea, fishy body odour (for L-carnitine)
Coenzyme Q10 10 mg/kg/day divided bid or tid (max 100 mg tid)	

Courtesy NASPGHAN: Incorporated from the NASPGHAN consensus statement [16] on CVS

every 1–4 weeks to achieve at least an average therapeutic dose for two CVS cycles (e.g. if monthly, then for 2 months). If any of the medication causes intolerable side effects and/or proves to be ineffective, then it is appropriate to switch to another medication. The common side effects tend to be dose related and may be addressed by reducing the dosage.

If a patient *does not* respond, consider the following:

- Diagnoses other than CVS and need for additional diagnostic testing
- Whether an adequate trial was administered (e.g. a high-end dose given for at least a two-cycle trial period) or there was lack of adherence
- Combination therapy of two medications (especially amitriptyline with one of the other main drugs)
- Complementary therapy such as carnitine, coenzyme Q, low oestrogen oral contraceptives, acupuncture
- Psychotherapy

Alternate Prophylactic Approaches

L-carnitine (commonly prescribed dose of 50–100 mg/kg/day, max 1 g), a nutrient that serves as a transport cofactor for long-chain fatty acids into mitochondria, may help patients with suspected mitochondrial or metabolic dysfunction and has a benign side effect profile.

There is anecdotal experience with coenzyme Q, low oestrogen oral contraceptives (particularly in menstrual related CVS), acupuncture and psychotherapy, but there's no data to support its use.

Supportive and Abortive Interventions

During the acute episode of vomiting, the supportive measures should be as follows:

- Placing children in less stimulating environments
- Replenishing fluids, electrolytes and energy
- Treating symptomatic nausea, vomiting and severe abdominal pain

Note: Early intervention within the first 2–4 h of onset either at home or at a hospital may be more effective than later intervention.

At all ages, use of intravenous 10 % dextrose and high-dose 5HT3 antagonist anti-emetics (e.g. ondansetron 0.3–0.4 mg/kg/dose every 4–6 h) is recommended to treat energy deficits and vomiting, respectively. If no enteral intake for 3–5 days, then initiate peripheral parenteral nutrition with 1.5 g of amino acids/kg/day and energy units above the catabolic threshold of 55–70 kcal/kg/day.

Only if 5HT3 antagonist anti-emetics are ineffective, then concomitant sedation with lorazepam (0.05–0.1 mg/kg/dose intravenously [IV] every 6 h) or diphenhydramine (1–1.25 mg/kg/dose I.V. every 6 h) is recommended. Severe abdominal pains are treated with parenteral acid suppression and/or nonsteroidal anti-inflammatory drugs or narcotics.

As an abortive approach, intranasal triptans may be used in children age 12 and older with infrequent (<1/month) or milder episodes (<24 h).

Once the vomiting starts, evaluation in an emergency department or direct admission to the hospital ward before dehydration ensues is appropriate in some patients for treatment protocols specifying intravenous fluids, medications and admission criteria.

Providing the patient with a letter that explains CVS and specifies an individualized management protocol can facilitate prompt institution of therapy. A template of such a letter can be found on the following weblink http://www.cvsaonline.org. Some behaviours during episodes may appear to be odd but are in fact common in CVS episodes. Many children become non-communicative and curl into a foetal position because, in their hypersensitive state, any further stimulation heightens their nausea and can trigger more vomiting. At best, the child should not be unnecessarily disturbed. There are other children who drink obsessively to induce vomiting. Reductions in these behavioural responses generally are observed when patients receive adequate symptom relief with antiemetics and sedation. Most patients with CVS will respond partially to one of the regimens discussed above. If a child does not respond, or the episode differs substantially from previous ones by greater severity, longer duration or new or different symptoms, then the clinician should reconsider the possibility of an underlying surgical lesion and the need for new or to repeat diagnostic testing (e.g. abdominal ultrasound, brain MRI).

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Reflux Esophagitis and the Child with Heartburn

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Mike Thomson

Heartburn or substernal burning pain is a symptom of GERD with or without esophagitis [1]. Recent consensus statements suggest that typical heartburn is a reliable indicator for GERD in adolescents and adults if it is the dominant symptom [2, 3]. Recent adult and pediatric consensus guidelines have applied the terms "typical reflux syndrome" or "reflux chest pain syndrome" to this presentation [2, 3]. One study in adults found that dominant heartburn had a positive predictive value of 81 % for GERD determined by pH study [4], but other studies have not confirmed this close association between history and test results [5]. Esophageal pH probe results are normal in one third of adults with chronic heartburn, even those whose heartburn is reproduced by esophageal acid perfusion and those who respond favorably to antacids. Some adults with heartburn and normal pH studies have endoscopically proven esophagitis [6]. In older children and adolescents, the description and localization of heartburn pain are probably reliable. In young children, however, symptom descriptions and localization may be unreliable [7–12].

GERD is often diagnosed clinically in adults based on a history of heartburn defined as substernal, burning chest pain, with or without regurgitation. Based on expert opinion, the diagnosis of GERD can be made in adolescents presenting with typical heartburn symptoms as in adults [3, 13–17]. However, a clinical diagnosis based on a history of heartburn cannot be used in infants, children, or nonverbal adolescents (e.g., those with neurologic impairment) as these individuals cannot reliably communicate the quality and quantity of their symptoms. The verbal child can communicate pain, but descriptions of quality, intensity, location, and severity generally are unreliable until at least 8 and possibly 12 years of age [7–11, 17].

As in adults, individual symptoms in children generally are not highly predictive of findings of GERD by objective studies. For example, in a study of irritable infants under 9 months of age, regurgitation >5 times per day had a sensitivity of 54 % and specificity of 71 % for a reflux index (RI) >10 % by esophageal pH testing, while feeding difficulties had a sensitivity of 75 % and specificity of 46 % [18]. A similar poor correlation of symptoms and esophageal acid exposure was observed during an omeprazole treatment study in irritable infants; similar reductions in crying occurred in both treated and untreated, infants and the extent of reduction crying did not correlate with extent of reduction of the RI in the treated patients [19].

Because individual symptoms do not consistently correlate with objective findings or response to medical treatment, parent or patient-reported questionnaires based on clusters of

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symptoms have been developed. Orenstein et al. [3, 20] developed a diagnostic questionnaire for GERD in infants. A score of >7 (of 25 possible) on the initial instrument demonstrated a sensitivity of 0.74 and specificity of 0.94 during primary validation. The questionnaire has undergone several revisions [16]. The questionnaire has been shown to be reliable for documentation and monitoring of reported symptoms. However, when applied to a population in India, it had a sensitivity and specificity of only 43 % and 79 %, respectively, compared to pH monitoring results [14]. In another study of infants referred for symptoms of reflux disease and controls, the questionnaire had sensitivity and specificity of 47 % and 81 % for an RI >10 % and 65 % and 63 % for a reflux index >5 %. The questionnaire score failed to identify 26 % of infants with GERD. The score was positive in 17 of 22 infants with normal biopsies and pH studies and in 14 of 47 infants with normal pH studies. No single symptom was significantly associated with esophagitis [13]. In another study, the questionnaire was unable to identify a group of infants responsive to proton-pump inhibitor therapy [21]. Thus, no symptom or cluster of symptoms has been shown to reliably predict complications of reflux or to predict those infants likely to respond to therapy.

A five-item questionnaire developed for children 7–16 years of age had a sensitivity of 75 % and specificity of 96 % compared to pH monitoring during primary validation [22]. No subsequent independent confirmatory validation has been performed. Other diagnostic questionnaires such as the GERD Symptom Questionnaire [15] have not been compared to objective standards like endoscopy, pH monitoring, or esophageal MII monitoring. Some researchers have used questionnaires to monitor symptoms of children during GERD therapy [23]. Whether this method is preferable to monitoring individual symptoms is uncertain. Although daily symptom diaries are frequently used in adults to monitor the effects of therapy, these have not been validated in children.

No randomized, placebo-controlled studies evaluate lifestyle changes or pharmacologic therapy of heartburn in children or adolescents. Case series have shown that PPI therapy relieves heartburn symptoms in adolescents [17, 23, 24]. Expert opinion suggests using a management approach to heartburn in older children and adolescents similar to that used in adults (Fig. 102.1). Other causes of heartburn-like chest pain including cardiac, respiratory, musculoskeletal, medication-induced, or infectious etiologies should be considered. If GERD is suspected as the most likely cause of symptoms, lifestyle changes, avoidance of precipitating factors, and a 2–4-week trial of PPI are recommended [12, 25–27]. If there is no improvement following empiric therapy, the older child or adolescent should be referred to a pediatric gastroenterologist for diagnostic evaluation. If improvement follows PPI therapy and lifestyle changes, treatment can be continued for 2–3 months. In some patients, abrupt discontinuation of treatment may result in acid rebound that precipitates symptoms; therefore, it is recommended that antisecretory therapy should be weaned slowly [28, 29]. If symptoms recur when therapy is weaned or discontinued, upper endoscopy may be helpful to determine the presence and severity of esophagitis and differentiate reflux-related esophagitis from non-reflux pathologies such as infection or eosinophilic esophagitis that may present with heartburn [30, 31]. Because chronic heartburn can have a substantial negative impact on quality of life, long-term therapy with PPI may be required, even in the absence of esophagitis [32, 33]. Extrapolation from adult data suggests that in older children and adolescents, on-demand or intermittent therapy with antacids, H2RA or PPIs, may be used for occasional symptoms of heartburn [33–36].

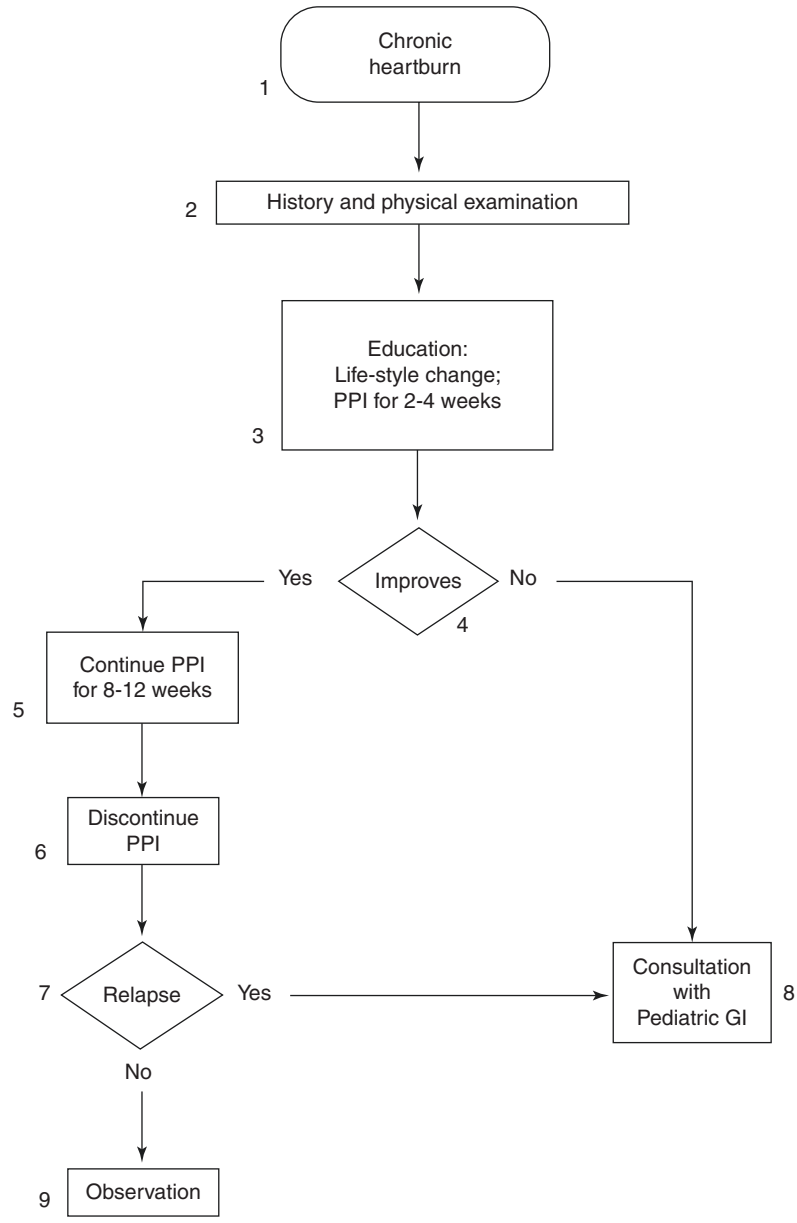

Fig. 102.1 Approach to an older child or adolescent with heartburn

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Food Refusal, Dysphagia, and Odynophagia

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Introduction

There has been significant advancement in our knowledge of the neurophysiology of swallowing. This fundamental sensorimotor function evolves from the primitive suck-swallow pattern first observed in a fetus to the more complicated adult biting-masticating-swallow pattern. The maturation process occurs in a complex and diverse cortical network which exists in the brainstem and controls the three primary phases of swallowing: oral, pharyngeal, and esophageal. Contribution of the latest neuroimaging techniques in understanding the complex swallowing process has been invaluable. For example, we now know that a normal swallow activates in the mid-lateral primary sensorimotor cortex bilaterally. Sensory input from the tongue and oropharyngeal mucosa is critical in the initiation of swallowing, while proper functioning of the cortical network and the striated muscles of the pharynx and esophagus is crucial for the sequence of motor events that result in a normal swallow. Disorders affecting any site along this pathway can result in dysfunctional swallowing or dysphagia, which in infants and toddlers may manifest as food refusal. Breakdown in the central integration of swallowing and airway protective reflexes can lead to aspiration, which may also present as food refusal.

Pediatric dysphagia may be transient, chronic, or progressive [1] depending on its etiology. It can occur as a result of structural or functional abnormalities in the sensorimotor pathways that control swallowing, behavioral or psychological disorders, or a combination of both. Structural abnormalities of the brain, oropharynx, and esophagus are easily identifiable using radiographic or endoscopic techniques. However, diagnosis of functional abnormalities in the neural pathways affecting swallowing is much more challenging, as there are currently no commercially available diagnostic markers or methods to test them.

Odynophagia or pain during swallowing is most commonly due to an inflammatory process in the oropharynx or esophagus, but occasionally may be related to an impediment in bolus movement. It must be distinguished from heartburn and dysphagia in older children as it may direct the clinician to the correct diagnosis. Although odynophagia may be a symptom of peptic esophagitis, it is more often associated with other conditions such as oropharyngeal inflammation, esophageal ulcer, eosinophilic esophagitis, infectious esophagitis, and pharyngeal or esophageal

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motor disorders. Even though it is conceivable that gastroesophageal reflux disease can cause odynophagia, there are no pediatric reports studying their association.

Food Refusal

It is challenging to diagnose dysphagia or odynophagia in infants and toddlers due to an inability to accurately communicate their symptoms. They typically develop behaviors around eating (food refusal) that may be a manifestation of dysphagia or odynophagia. In these younger children, common signs and symptoms of a swallowing problem include vomiting, coughing, choking, aspiration, lack of interest in eating, straining or extension of muscles during feedings, extensive time required to feed (more than 30 min), failure to thrive, choking, coughing or gagging with feeds, and presence of tongue thrusting during swallowing [2]. It has been estimated that 25 % of normal infants and 80 % of young children with developmental disabilities demonstrate infant feeding disorders [3]. Food refusal is considered severe in 1–2 % of infants, resulting in serious deficits in growth and development which persist into childhood in 70 % of the cases [3]. Since the etiology of feeding disorders in young children is usually multifactorial, including neurobehavioral and psychosocial, and has a significant impact on the family, an interdisciplinary approach to address it is warranted. The team should include members from speech and language pathology, occupational therapy, nutrition, child psychology, and a physician with expertise in the field.

Based on a review of 126 children seen at Cincinnati Children's Hospital Medical Center's (CCHMC) Interdisciplinary Feeding Clinic from 2008 to 2009, we found that most children were males and had been of full-term gestational age (see Table 103.1). This may be due to preterm infants being managed at a high-risk clinic during their first year of life. The most common comorbid conditions in the full-term group were gastrointestinal disorders, while in the preterm group was neurodevelopmental disorders. Both groups underwent a variety of diagnostic studies. The top 4 most commonly ordered tests were videofluoroscopic swallow study (VFSS), esophagogastroduodenoscopy (EGD), upper gastrointestinal (UGI) contrast study, and fiberoptic endoscopic evaluation of swallowing (FEES). The average percentage of abnormal results among these studies was 43 % in the preterm children and 55 % in the full-term group. Among the less commonly ordered studies, which include rigid microlaryngobronchoscopy (MLB), flexible bronchoscopy (FB), gastric emptying scan, and brain MRI, the average percentage of abnormal results was 89 % in the preterm group and 68 % in the full-term group. The lower yields of VFSS, EGD, UGI, and FEES may indicate their role as screening tools. The higher percentage of abnormal results among the less commonly ordered studies highlights the importance of choosing the appropriate diagnostic study in the evaluation of pediatric food refusal, so as to reduce the number of unnecessary tests.

Food refusal in infants and toddlers may signify the presence of dysphagia or odynophagia due to a wide spectrum of disorders or disease states. To interpret the clinical manifestations, the clinician needs to consider the age, past medical or surgical history, and a thorough account of the patient's feeding behavior. Table 103.2 depicts a proposed algorithm for the evaluation of food refusal in children.

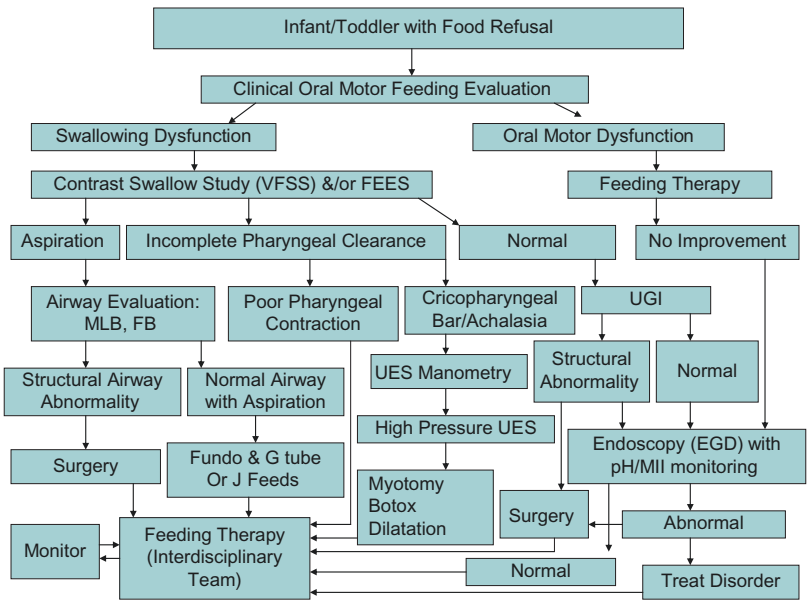
If the child demonstrates food refusal or unusual feeding behaviors, he should undergo an initial clinical oral motor feeding assessment by a speech language pathologist or occupational therapist. If the initial assessment is suggestive of a purely oral motor dysfunction, then the treatment would proceed to oral motor feeding therapy. Strategies employed during feeding therapy sessions include postural (compensatory) changes, utensils of different shapes and sizes, liquids and solids of different consistencies, and textures and behavioral modifications. Should there be no improvement in the child's feeding refusal after successive therapeutic sessions, then a more in-depth evaluation with an upper endoscopy may be indicated.

If the initial assessment by the therapist is indicative of a swallowing dysfunction, then a VFSS is recommended. This contrast swallow study may demonstrate delayed swallow

Table 103.1 Clinical profile of children evaluated by the interdisciplinary feeding team at CCHMC

	Preterm		*Full term*	
Total 126 (*n*; % of total)	31 (25%)		95 (75%)	
Males (%)	74		61	
NG tube for initial feeds (%)	57		13	
Mean age at 1st clinic visit	35 months		31 months	
Mean weight at 1st clinic visit	9.5 kg		9.3 kg	
Orally fed at 1st clinic visit (%)	70		72	
Therapy prior to 1st clinic visit (%)	52		59	
Speech delay (%)	48		35	
Most common comorbid condition	Neurodevelopmental		Gastrointestinal	
2nd most common comorbid condition	Gastrointestinal		Neurodevelopmental	
Diagnostic studies	*Patients* (*n*)	*Abnormal* (%)	*Patients* (*n*)	*Abnormal* (%)
VFSS	11	45	46	65
EGD	11	45	46	39
UGI contrast study	7	43	27	37
FEES	6	33	29	82
Rigid MLB	2	100	20	80
Flexible bronchoscopy	2	100	13	85
Gastric emptying scan	3	66	7	14
MRI brain	2	100	17	65

Table 103.2 Algorithm for evaluation of food refusal in children



initiation, shallow penetration, deep penetration, aspiration, presence of a protective response, and also if any compensatory strategies are effective in making the swallowing more efficient. If the compensatory strategies alleviate the issue and there is no risk of aspiration, then further airway evaluation with MLB, FB, or FEES is not always necessary. If the contrast swallow study demonstrates incomplete pharyngeal clearance that is not alleviated by compensatory strategies (such as additional swallows, alternating between solid and liquid states, and chin tuck), then this

may be an indication of oral motor weakness and poor pharyngeal contraction. The child subsequently should proceed to feeding therapy. Other causes of incomplete pharyngeal clearance may be upper gastrointestinal motility disorders, including cricopharyngeal achalasia. If the upper esophageal sphincter (UES) manometry study shows a consistently elevated baseline pressure of the UES, then therapy can include esophageal botulinum toxin (Botox) injection, dilatation, or myotomy. If the VFSS is otherwise normal, then the clinician should rule out structural abnormalities that may be causing behaviors of food refusal. An UGI series or endoscopy may reveal an anatomic anomaly such as an esophageal web, stricture, or hiatal hernia that may need surgical intervention. It is well recognized that even after surgical correction or adequate medical treatment of the underlying disorder, children may continue to be orally aversive. Persistence of food refusal despite resolution of the etiologic disorder is believed to be due to a learned response that can be addressed by appropriate therapy and monitoring by an interdisciplinary feeding team.

Aspiration

Aspiration is the entry of foreign material into the airway, below the true vocal folds, and represents a breakdown of the airway protective mechanism (such as esophago-glottal and pharyngo-glottal closure reflexes). It is in contrast to penetration, which involves entry of foreign material into the larynx above the true vocal folds [4]. Aspiration occurs when the airway protective reflexes are compromised as a result of either a structural defect of the laryngeal structures or a functional abnormality. In healthy, awake, and alert individuals, aspiration should result in coughing to expectorate the foreign material. Silent aspiration is aspiration that is not associated with a cough response when an individual is awake and alert [5]. Aspiration of material into the airway can occur from above during swallowing or from below due to refluxed gastric contents. Several studies have shown that oropharyngeal dysfunction with silent aspiration may occur in otherwise healthy children without known risk factors, such as neurodevelopmental delay, gastroesophageal reflux, or overt feeding difficulties [6]. Both forms of aspiration can result from reduced oral control, pharyngeal delay, reduced laryngeal elevation, and esophageal reflux [5]. Many infants who aspirate may not cough [7]. Feeding refusal or unexplained chronic lung disease may be the only symptom of aspiration in an infant or toddler. Aspiration commonly manifests as chronic respiratory symptoms (such as wet cough, choking, gagging, and gurgling noises) during or after feedings [2]. Therefore, early identification and appropriate treatment may reduce the ensuing morbidities associated with swallowing dysfunction and chronic aspiration [8].

Evaluation for aspiration should begin with a detailed medical, developmental, and feeding history [9]. Clinical evaluation should include observation of a typical feeding. Ideally this should be performed by an interdisciplinary team with a speech pathologist, occupational therapist, or nurse with expertise in infant or childhood feeding disorders [1]. The knowledge of the existence and frequency of silent aspiration became evident with the use of videofluoroscopic swallow study (modified barium swallow study). In addition to identifying aspiration, it can also define anatomic or physiologic disorders. Fiberoptic endoscopic evaluation of swallowing (FEES) is another modality for assessing swallows and is performed by an ENT physician while the patient is awake [5]. In addition to visualizing the anatomy and function of the pharynx and larynx with swallows, it can also test for sensation of the region and vocal fold movement. The findings of the two studies often complement each other and give a better understanding of the swallowing process. If a structural laryngeal defect, such as a laryngeal cleft, is suspected, then a rigid microlaryngobronchoscopy may need to be done to confirm the finding before surgical intervention to correct the defect is contemplated. A flexible bronchoscopy with bronchoalveolar lavage (BAL) may be indicated to assess the severity of aspiration by visualizing the mucosal lining of the tracheobronchial tree, secretions, and lipid-laden macrophages in the lung washings. Pepsin

analysis may also be performed on the washings to assess aspiration of gastric contents, as pepsin is exclusively produced in the stomach.

Evaluation and management of a child with aspiration should be done by an interdisciplinary team that includes physicians from otolaryngology, pulmonology and gastroenterology, feeding therapist or speech pathologist, and nutritionist. There are six major issues that need to be addressed by the team including (1) normalization of posture and tone, (2) adaptation of food and feeding equipment, (3) oromotor therapy, (4) feeding therapy, (5) nutritional support, and (6) management of associated disorders [1]. In the event that no surgically correctable structural defect of the upper aerodigestive tract is identified in a child with clinically significant aspiration, oral feedings may need to be withheld and alternative enteral routes for feeding considered. If aspiration occurs only with certain consistencies, then feeds may need to be modified such that the risk for aspiration is minimized. Other strategies such as pacing during feeds and using special feeding utensils are often employed by therapists to avoid aspiration. The team nutritionist should closely follow the child's growth parameters and diet to ensure adequacy of vitamin, mineral, and caloric intake. With time, differential growth of the larynx and oropharyngeal structures reduce the risk for aspiration; and children with milder forms of aspiration and the associated feeding disorder tend to improve.

Causes of Dysphagia and Odynophagia

Older children are more likely to complain of symptoms of dysphagia and odynophagia. The more commonly diagnosed causes are listed in Table 103.3.

Table 103.3 Causes of dysphagia and odynophagia in children

Esophageal causes
1. Eosinophilic esophagitis
2. Gastroesophageal reflux disease (NERD, ulcer, stricture, Barrett's)
3. Pill esophagitis
4. Infectious esophagitis: fungal, viral, bacterial, tuberculosis
5. Foreign body ingestion
6. Rheumatic esophageal disorders: pemphigus, epidermolysis bullosa, dermatomyositis, lupus, systemic sclerosis
7. Esophageal tumors
8. Mucositis (chemotherapy)
9. Congenital esophageal rings and webs
10. Esophageal motor disorders
11. Post operative: fundoplication, cardiac surgery, TEF/EA
Extra-esophageal causes
12. Pharyngitis, laryngitis, tonsillar, or adenoidal hypertrophy or inflammation
13. Vascular compression (dysphagia lusorum)
14. Compression from mediastinal mass
15. Psychogenic
16. Other: hypothyroidism, hyperthyroidism, pellagra, vascular malformation

Eosinophilic Esophagitis

Of the mucosal disorders, eosinophilic esophagitis is now increasingly recognized to be a more common cause of dysphagia and odynophagia than gastroesophageal reflux disease (GERD) [10]. Eosinophilic esophagitis (EE) is defined as a primary clinicopathologic disorder of the esophagus [11]. It is characterized by esophageal and/or upper gastrointestinal tract symptoms, esophageal mucosal biopsy specimens containing greater than or equal to 15 intraepithelial eosinophils per high power field in one or more biopsy specimens, absence of pathologic GERD based on a normal pH monitoring study of the distal esophagus, or lack of response to high-dose PPI medication. Eosinophilic inflammation appears to be chronic, but symptoms may be persistent or relapsing.

Clinical manifestations of EE in pediatric patients vary by age [11]. Younger children often present with feeding refusal because they are unable to convey the feeling of dysphagia [12]. Children may also describe GERD-like symptoms, such as heartburn and regurgitation. Complaints of emesis (occasionally cyclic),

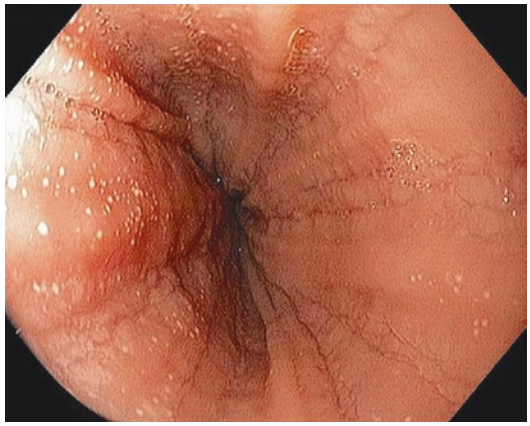


Fig. 103.1 Eosinophilic esophagitis with linear furrowing, edema, longitudinal shearing, raised white specks, whitish exudates, "crepe paper mucosa"

abdominal pain, dysphagia, and food impaction increase with age. Less common manifestations of EE include failure to thrive, weight loss, chest pain, and diarrhea. In the largest longitudinal study consisting of 381 children with EE, Liacouras reported most children presented with GERD symptoms or dysphagia refractory to acid-suppression treatment [13].

There is a higher prevalence of EE in males than females. It has been described in a variety of ethnic backgrounds, including white, African-American, Latin, and Asian; but it remains unclear whether EE has a racial predilection. A higher prevalence of food allergies, asthma, and eczema has also been reported in children with EE [14]. The socioeconomic distribution and seasonal variation of EE has not been systematically studied. This disease has not been shown to decrease life expectancy.

Diagnosis consists of an esophagogastroduodenoscopy (EGD) to identify a number of gross mucosal abnormalities, including longitudinal furrowing, friability, edema, longitudinal shearing, raised white specks, whitish exudates, "crepe paper mucosa," narrow caliber esophagus, Schatzki ring, felinization, and transient or fixed rings [11] (see Fig. 103.1). None of these features are pathognomonic for EE. But in the appropriate clinical context, the presence of more than one of these findings strongly suggests EE. On the other hand, EE patients can also present with grossly normal-appearing mucosa. In Liacouras' study of 381 children with EE, 30 % had an endoscopically normal-appearing mucosa [13]. Therefore, biopsy specimens from the esophagus should be obtained regardless of the gross mucosal appearance. A retrospective analysis of 341 biopsy specimens from 66 adults with EE showed that one biopsy specimen had a sensitivity of 55 %. This was in contrast to a sensitivity of 100 % with five biopsy specimens [15]. Multiple biopsy specimens should therefore be obtained from the proximal, middle, and distal esophagus, in addition to those obtained from the stomach and duodenum to rule out other diseases, such as eosinophilic gastroenteritis and inflammatory bowel disease [11].

Other diagnostic recommendations include an UGI contrast study to identify the presence of an esophageal stricture or other possible anatomic causes for vomiting (e.g., malrotation, hiatal hernia) [11]. The contrast study may also be beneficial in subsequent endoscopies by alerting the endoscopist to use a smaller caliber endoscope or to proceed cautiously in order to avoid a mucosal tear. It also allows the endoscopist to prepare for an esophageal dilatation if indicated [11].

Based on the current diagnostic criteria from the First International Gastrointestinal Eosinophilic Research Symposium Consensus Statement in 2007 for EE, an empiric trial of 6 to 8 weeks of acid-suppression therapy with a proton-pump inhibitor (2 mg/kg/day divided twice a day to a maximum of 40 mg twice a day) is necessary before performing an EGD [16]. Acid from gastroesophageal reflux can also trigger esophageal eosinophilia, but at a much lower degree than that caused by EE [17]. The mainstays of EE treatment are avoidance diets, anti-inflammatory medications, and endoscopic dilatations when strictures are present [17].

Directed elimination diets are often used before considering an elemental diet. They have been shown to be effective in approximately 70 % of EE patients [18, 19]. In a cohort of 35 EE patients, Kagalwalla et al. showed that approximately 74 % responded symptomatically and histologically to the removal of the six most likely foods to cause EE: dairy, soy, egg, wheat, peanut,

and shellfish [20]. Although elimination diets are effective, strict elemental diets have demonstrated a significantly greater response. Case series data in both adults and children support a 92–98 % patient response to amino acid-based elemental formula with both symptomatic and histologic improvement [18, 21]. The elemental formula can be administered either orally or via nasogastric or gastrostomy tube. A repeat EGD is then performed in 4–6 weeks to establish histologic improvement. Foods are then reintroduced sequentially, beginning with the least allergenic [16]. Endoscopic surveillance is repeated after the reintroduction of five to seven new foods. Although dietary therapy is highly effective, the psychosocial impact and quality of life issues on the patient and family must be strongly considered before implementing this mode of therapy.

Topical corticosteroid therapy with swallowed fluticasone is a mainstay of therapy in EE patients. In a randomized placebo-controlled trial of topical therapy with swallowed fluticasone versus oral prednisone [22], each group demonstrated symptomatic and histologic improvement in excess of 90 % of patients. Therefore, high-dose topical, swallowed corticosteroids may be as effective as systemic corticosteroids with less toxicity. Oral viscous budesonide is another steroid preparation that has demonstrated success in pediatric EE patients. Aceves et al. reported an 80 % histologic and symptomatic response in a case series of 20 pediatric EE patients [23]. The disadvantages of using topical steroids are incomplete treatment of the disease, as EE recurs when the treatment is discontinued, and development of side effects, such as esophageal candidiasis [16]. When using topical, swallowed corticosteroids, patients cannot eat, drink, or rinse their mouth for 20–30 min after taking the medication. Other topical therapies, such as cromolyn sodium and leukotriene receptor antagonists, have not been proven to be very successful in the treatment of EE [13]. Currently biologic agents that target the eosinophilic inflammatory cascade, such as anti-IL-5 therapy [24], are in various stages of development and clinical trials.

Although endoscopic esophageal dilatation is indicated for peptic strictures, it should be avoided for most EE patients because of a higher rate of esophageal perforation [25]. Esophageal dilatation is effective for immediate symptomatic improvement for food impaction. It is not recommended as first-line therapy due to concerns of pain, bleeding, perforation, and not addressing the underlying pathogenesis [16]. As a general rule, other modes of therapy should be used before performing dilatation, and an UGI series prior to dilatation may be helpful in identifying the precise location and characteristic of the stricture.

Gastroesophageal Reflux Disease (GERD)

Gastroesophageal reflux (GER) is a physiologic phenomenon that occurs more frequently in infants than older children. Gastroesophageal reflux disease (GERD) in pediatric patients is defined as the reflux of gastric contents into the esophagus that cause troublesome symptoms and/or complications. Symptoms of GERD vary by age. Description of symptom intensity and localization may be unreliable until the age of 8 years or older [26]. The definition of when GER becomes “troublesome” remains challenging in infants and children, who may not manifest an objective complication of GERD clinically. Abnormal crying due to some other cause may be mistaken for GERD. Alarming symptoms include weight loss, dysphagia, bleeding, anemia, choking, failure to thrive, and feeding difficulties [27]. The physiologic basis for most GER episodes is transient lower esophageal sphincter relaxation (TLESR). This brief relaxation of the lower esophageal sphincter (LES) can be triggered by distension of the gastric fundus and is mediated via the vagus nerve [28]. TLESR can result in reflux of air (belch), liquid, solid, or mixed gastric contents into the esophagus.

In the pediatric age group, GER was regarded as the most common organic cause of esophagus-related pain [29] until EE became more prevalent. Reflux decreases the threshold for perception of visceral pain [30]. Risk factors for severe reflux include CNS impairment, esophageal atresia,

chronic lung disease, diaphragmatic hernia, and hiatal hernia. In children, dysphagia may be the presenting symptom of GERD-related esophagitis even in the absence of a history suggestive of gastroesophageal reflux [31]. Dysphagia is a symptom in more than 30 % of adults with GERD [32].

Infants with crying and feeding disorders are perceived as more vulnerable by their parents. Depending upon parental perceptions, experience, coping skills, and psychosocial conditions, these infants are often brought to medical attention. Infants seen in clinic for a complaint of crying and fussiness had more feeding difficulties, were less responsive to treatment, and had more maternal stress [33]. Most infants with physiologic regurgitation (spit-ups) resolve without intervention. A follow-up study showed that infants who regurgitated at 6–12 months of age were no longer doing so a year later [34]. When given a history of "vomiting," it is important to differentiate between regurgitation and vomiting, since the latter is more likely to be pathological and may need to be evaluated more urgently. Unlike vomiting, regurgitation has no CNS emetic reflex, retrograde intestinal contractions, nausea, or retching. However, due to a short esophagus in infants, most reflux episodes tend to project as "vomiting" and are commonly reported as such by parents. A history of regurgitation is neither necessary nor sufficient for a diagnosis of GERD due to lack of sensitivity and specificity [26].

When compared to older children, those less than 5 years of age with GERD tend to present more often with food refusal, regurgitation, vomiting, and abdominal pain [35]. Young children with a history of vomiting after feeding (due to GERD or other reasons) may have difficulty in accepting feeds, despite having no alteration of oral and pharyngeal phases of swallowing [36]. The proposed hypothesis is that initial acid exposure of the mucosal chemoreceptors and nerve endings in the esophagus send afferent signals to the spinal nerves that are transmitted to the brain, which perceives the sensation as pain or discomfort. The neurochemical alterations induced in this pathway appear to persist even after the initial noxious stimulus (vomiting, GERD) has resolved and leaves the child with a hypersensitivity to any bolus movement along the esophagus, including the swallowing of food. Peripheral and central sensitization are believed to be important mechanisms for this ongoing heightened perception of esophageal sensation (visceral hypersensitivity) [4] resulting in food refusal.

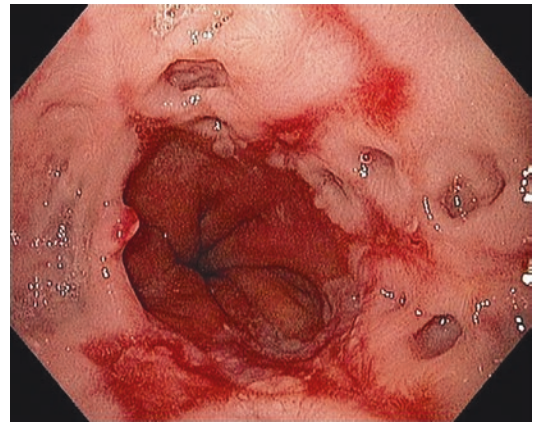


Fig. 103.2 Erosive esophagitis from gastroesophageal reflux disease (GERD)

Older children are able to give an appropriate history of heartburn and regurgitation, thereby making the diagnosis of GERD easier. In adolescents the underlying pathophysiology and symptom presentation of GERD are similar to adults. For unclear reasons, non-erosive reflux disease is more common in symptomatic children with GERD [37]. Complications of GERD such as erosive esophagitis (see Fig. 103.2) and peptic stricture (see Fig. 103.3) are more commonly observed in children with neurodevelopmental delay. A pediatric study showed the prevalence of esophagitis was higher in children with H. pylori as compared to children without H pylori. The prevalence of H pylori was higher in patients over 10 years of age when compared to younger children [38].

In a child with dysphagia or odynophagia, an UGI series is usually the first recommended test. This is not useful for the diagnosis of GERD, but it can evaluate for anatomic abnormalities of the upper gastrointestinal tract which may explain the GERD-like symptoms. If the initial history is suggestive of esophagitis (odynophagia), an upper endoscopy may be performed as the initial diagnostic test [10].

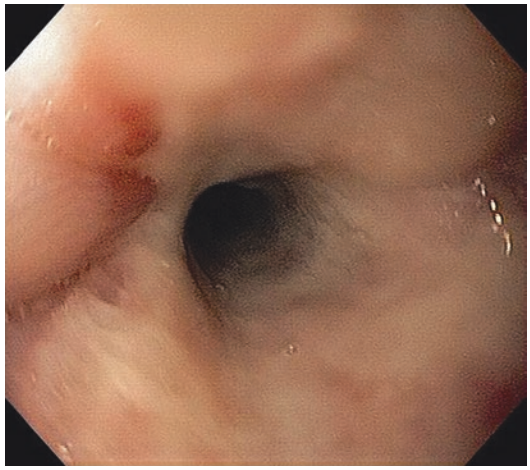


Fig. 103.3 Esophageal stricture from GERD

In infants and children with neurodevelopmental disabilities, a thorough evaluation of the oral, pharyngeal, and esophageal phases of swallowing is imperative when the presenting symptom is dysphagia or food refusal. The VFSS is used to evaluate the oropharyngeal and upper esophageal phases of the swallow. In a study of 186 children with neurologically based dysphagia, aspiration was observed in 48. Of these, 94 % had "silent" aspiration with no objective clinical feature to suggest that these children were at risk for aspiration-related complications [39].

Combined pH/multichannel intraluminal impedance (pH/MII) is being increasingly utilized for the diagnosis of GERD. pH/MII detects bolus movement along the esophagus via multiple impedance measuring sites. It can differentiate between swallowed material and reflux events, and acid and nonacid reflux and detail the mechanism of bolus clearance, acid clearance, proximal extent of a reflux episode, and symptom association [40]. Before pH/MII became available, esophageal pH monitoring was accepted as the gold standard for diagnosis of GER. Although studies have proven the superiority of pH/MII [41], the lack of normative data for children has prevented pH/MII to be widely accepted as the gold standard in the diagnosis of GERD. It is our opinion that pH/MII plays a key role in the evaluation of pediatric patients suspected of having GERD, especially in those less than 8 years of age with atypical symptoms.

An EGD is usually indicated to rule out other causes of esophagitis, such as pill esophagitis, Crohn's esophagitis, eosinophilic esophagitis, and infectious esophagitis. Endoscopy is often necessary in children since there is poor correlation between symptoms and endoscopic esophageal findings [42]. The prevalence of erosive esophagitis has been found to increase with age and is more common in adult males. Additionally, the only endoscopic finding in children that predicts the presence of erosive esophagitis is a hiatal hernia [42]. This is consistent with adult studies which show that lower esophageal sphincter pressure and amount of esophageal exposure to acid are poor predictors for disease severity and that presence of a hiatal hernia exerts a much stronger influence in the severity of erosive reflux esophagitis [34].

No studies have supported empiric therapy for GERD as a valid diagnostic test. Treatment without prior diagnostic evaluation is therefore not recommended in the infant with feeding refusal because it is often multifactorial; and there is no compelling evidence to support a causal relationship between infant feeding difficulties and GERD [10]. Behavioral feeding problems are common in healthy toddlers (9 % reported). These children are often misdiagnosed with GERD and treated with acid-suppression medications. One year follow-up of symptoms of GER during infancy showed no significant difference between cases and controls in feed refusal, irritability with feeding, back arching, choking or gagging, and abdominal pain [43]. Milk protein allergy can sometimes present early with symptoms similar to GERD. An empiric trial with an elemental formula or nursing after the mother has been on a 2-week dairy-free diet can be tried [10]. If feeding evaluation by an interdisciplinary team indicates that food refusal is a result of pain resulting from visceral hyperalgesia or reflux esophagitis, it is imperative to address the acid reflux in order to halt ongoing sensitization of the neural pathways and thereby remove the pain associated with eating [44]. This process of "desensitization" and addressing the learned avoidance response to feedings by an interdisciplinary team often takes time. Histamine-2

blockers and proton-pump inhibitors (PPI) have been prescribed for infants and toddlers even though the FDA has not yet approved PPI use in infants in the USA. Our unpublished data comparing acid reflux episodes using impedance technology in 150 infants either on ranitidine, lansoprazole, or no medications showed a statistically significant decrease in acid reflux events in infants who were on PPI compared to those on ranitidine or no medications. The total number of reflux episodes (acid and nonacid), however, was no different among the three groups.

In an older child with typical reflux symptoms suggestive of GERD, an empiric trial of a proton-pump inhibitor (PPI) for up to 4 weeks is justified. But improvement of heartburn following treatment does not confirm a diagnosis of GERD, as symptoms may improve spontaneously or by placebo effect. When a decision is made to treat GERD, a PPI is usually the treatment of choice. Those currently approved for use in children in the USA are omeprazole, lansoprazole, and esomeprazole. For children with erosive esophagitis, PPIs should be prescribed as initial therapy for 3 months. Pantoprazole has been shown to be effective in reducing endoscopically proven GERD in children [45].

Duodenogastroesophageal (bile) reflux may play a role in the pathophysiology of GERD and esophagitis that is refractory to PPIs [46]. A long-term follow-up study of infants with early feeding refusal showed no increase in disturbing eating habits, lower BMI, or lower self-esteem in adolescence than compared with infants without a history of feeding refusal [47].

Infectious Causes of Dysphagia and Odynophagia

Acute Pharyngitis/Tonsillitis, Retropharyngeal Abscess, and Other Deep Neck Abscesses

An acute onset of dysphagia is highly suggestive of an infectious process. One of the most common examples of this is acute pharyngitis. Typical presentations include severe odynophagia, throat pain, fever, and general malaise. Treatment is directed toward group A beta-hemolytic streptococcus, although viral infections are possible. For recurrent episodes, elective tonsillectomy has been recommended. Despite appropriate antibiotic therapy, acute tonsillitis can progress to a peritonsillar abscess, and surgical intervention may be necessary [48].

An infection of the retropharyngeal space is another cause of acute dysphagia in children. A typical presentation may include fever, irritability, dysphagia, torticollis, and/or drooling. Physical examination often reveals unilateral posterior pharyngeal swelling. Other common areas of infection or abscess are peritonsillar, retropharyngeal, submandibular, buccal, parapharyngeal, and canine space infections. Diagnostic imaging studies to delineate the lesion include lateral neck films, CT, and MR imaging. Treatment should include empiric antibiotic therapy to cover both gram-negative, gram-positive, and anaerobic organisms. Surgical intervention may be indicated as determined by the clinical course [49]. Treatment is surgical drainage of the abscess with paramount care given to the patient's airway [50].

Infectious Esophagitis

Esophageal inflammation could result from fungal (*Candida*), viral (herpes, cytomegalovirus), or bacterial infection. Historic risk factors for *Candida* esophagitis include immunosuppression, chronic inflammatory conditions requiring steroid use, diabetes mellitus, and antibiotic use [51]. In patients with these risk factors and symptoms of dysphagia, this diagnosis should be entertained. Physical examination may reveal white patches in the throat, which is highly suggestive of this etiologic agent. Diagnosis by an endoscopic evaluation may be necessary if risk factors are present. Endoscopic findings include an erythematous mucosa covered with white plaque-like lesions (see Fig. 103.4). Recommended treatment regimens include nystatin, ketoconazole, amphotericin, or fluconazole for at least 3 weeks.

Other causes of acute infectious esophagitis are herpesvirus and cytomegalovirus. Common presentations include fever, odynophagia, and

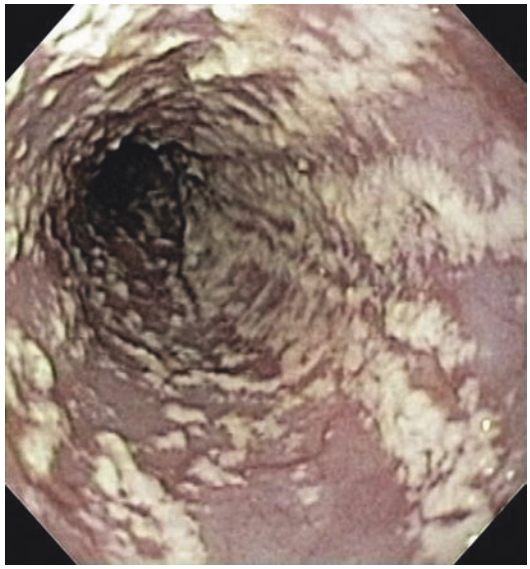


Fig. 103.4 *Candida* esophagitis with an erythematous mucosa covered with white plaque-like lesions

retrosternal pain of acute onset [52]. HSV esophagitis is a common infection in the immunocompromised host, but is also described in the immunocompetent patient. EGD is the diagnostic procedure of choice, since it allows for sampling for histology, culture, and tissue PCR. The endoscopic appearance may reveal vesicles, which are the earliest manifestation. The lesions then coalesce to form ulcers (usually less than 2 cm), frequently with normal-appearing intervening mucosa (see Fig. 103.5). Ulcers are well circumscribed and have a "volcano-like" appearance. In contrast, ulcers in CMV infection tend to be linear or longitudinal and deeper. Erythema, exudates, and erosive esophagitis are also commonly present [53]. Treatment usually involves supportive care in immunocompetent hosts as HSV esophagitis is a self-limited infection [52]. Immunocompromised hosts should be treated with a longer duration of therapy than is typically given for less invasive HSV infection (i.e., genital HSV). Acyclovir (400 mg PO five times a day for 14–21 days) is effective and has few side effects. Parenteral antiviral therapy, pain management, intravenous hydration, and/or nasogastric feeding may be indicated if symptoms of dysphagia and odynophagia are severe.

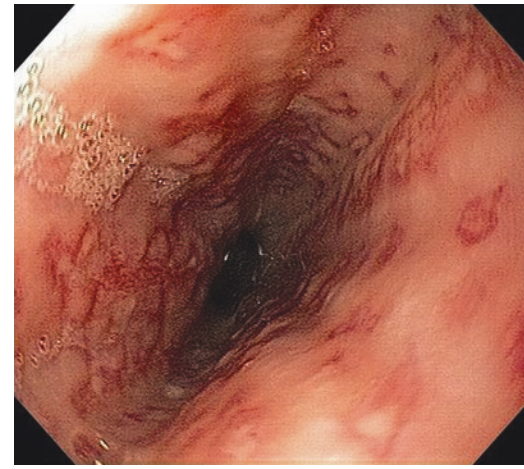


Fig. 103.5 Herpes esophagitis

Pill Esophagitis

Pill-induced injuries or pill esophagitis occur when caustic medicinal pills dissolve in the esophagus rather than passing rapidly into the stomach as intended [54]. The high concentration of active medication in pills is more likely to injure susceptible tissue if delivered to the wrong organ, in particular the esophagus. This type of injury is unfortunately common. Odynophagia is the hallmark of pill esophagitis [54]. The typical patient has no previous history of esophageal disease or symptom and presents with the sudden onset of odynophagia with or without dysphagia. Older patients may perceive that a pill has become lodged [54]. Complaints of retrosternal or substernal chest pain are also common [55]. The physician may elicit clues by careful questioning of whether little or no fluid was taken with the pill or if it was taken at bedtime or while reclining. Less typical symptoms are burning pain, which may suggest GERD, and gradually progressive pain, which may suggest an infectious etiology. Hemorrhage can occur, especially when the esophageal injury is due to nonsteroidal anti-inflammatory drugs (NSAIDS). Cases of hemorrhaging can be life-threatening, as esophageal ulcers have been known to penetrate the left atrium and major vessels. Esophageal perforation and mediastinitis have been attributed to medications such as sustained-release ferrous

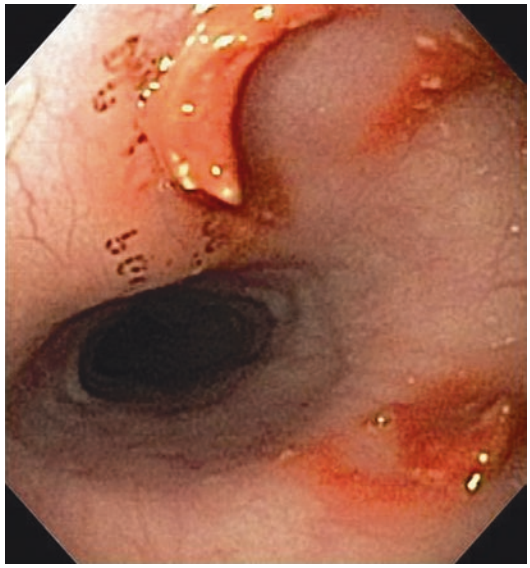


Fig. 103.6 Pill esophagitis with a discrete ulcer with normal surrounding mucosa

sulfate, sodium valproate, and aspirin-caffeine compounds. Other commonly implicated medications include sustained-release potassium preparations, tetracyclines, antivirals, quinidine, and bisphosphonates.

Diagnostic testing may be avoided if the presentation is typical and uncomplicated. A careful history and examination are required to rule out complications of pill esophagitis and to permit planning an alternative to the implicated oral medication. The mainstays of treatment are immediate discontinuation of the offending agent and supportive care. If symptoms progress or persist despite these measures and the diagnosis is in question, then the principle diagnostic modalities are double-contrast barium esophagram and an EGD [55]. An EGD is also indicated when hemorrhaging is involved or the patient is immunocompromised [54]. The typical endoscopic appearance of pill-induced esophageal injury is a discrete ulcer with relatively normal surrounding mucosa [56] (see Fig. 103.6). Endoscopy is much more sensitive than barium esophagram for subtle mucosal lesions. Furthermore, endoscopic biopsy and brushing are more likely than an esophagram to yield definitive alternative diagnoses such as GERD, neoplasia, or infectious esophagitis. The higher yield and accuracy make endoscopy the diagnostic procedure of choice, but it should be reserved for atypical cases as mentioned above [54]. Common sites of injury from pill esophagitis are at the junction of the proximal and middle thirds of the esophagus where the aortic arch compresses the esophagus and the lower esophagus above the LES.

Medical management of moderate to severe cases includes sucralfate to coat, protect, and promote healing of the ulcerated esophageal mucosa and acid-suppression therapy if GERD is felt to have played a role in the pathogenesis of the illness [55]. Rare cases involving hemorrhage or esophageal perforation early in the disease course may require therapeutic endoscopy or surgical intervention. Late complications include esophageal strictures that may require therapeutic endoscopy or bougienage [55].

Foreign Body Ingestion

Ingestion of foreign bodies is a common pediatric problem, with more than 100,000 cases occurring each year [57]. The vast majority of pediatric foreign body ingestions are accidental. In the USA and Europe, coins are the most commonly ingested foreign bodies. Other objects include toys, sharp objects such as needles and pins, batteries, chicken and fish bones, and food. Presenting symptoms vary by foreign body type, size relative to the patient, location of ingestion, and duration of impaction [58]. Children may present with a variety of symptoms, including choking, drooling, dysphagia, odynophagia, chest pain in older children, poor feeding, or respiratory symptoms, especially in younger patients, due to tracheal compression or esophageal erosion [59]. Eighty to 90 % of ingested foreign bodies pass spontaneously. Unsuspecting parents of younger children, who cannot give a history, will oftentimes find a foreign body that has been swallowed and ultimately passed in the diaper. Ten to 20 % of ingested foreign bodies require endoscopic removal; and less than 1 % require surgical intervention [58]. Serious complications, including obstruction and perforation,

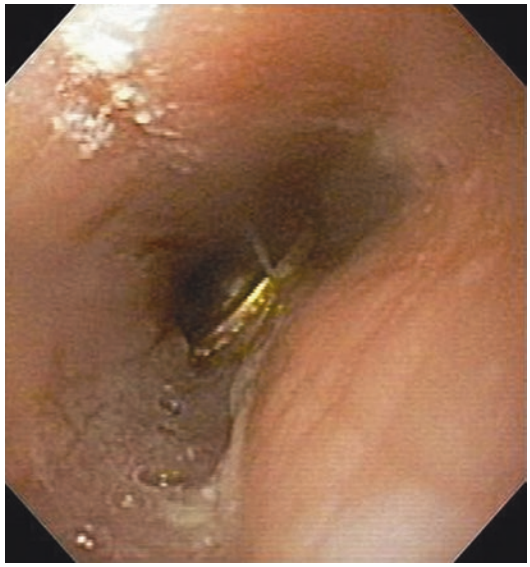


Fig. 103.7 Penny lodged in esophagus

are more likely with large, long, and sharp foreign bodies.

Management strategies are also based on the ingested foreign body type, location, and the patient's size. A radiograph should be obtained in every case of suspected radiopaque foreign body ingestion. When a coin is found in patients with respiratory symptoms lasting more than a few days, the possibility of esophageal erosion by the coin should be suspected. These coins may be difficult to remove endoscopically, require additional diagnostic imaging such as CT, and require the assistance of a pediatric otorhinolaryngologist using rigid instruments for removal. Approximately 60–70 % of esophageal coin impactions occur at the upper esophageal sphincter or thoracic inlet, 10–20 % lodge in the mid-esophagus at the level of the aortic notch, and 20 % sit just above the lower esophageal sphincter (see Fig. 103.7). Patients at increased risk of a retained esophageal coin include those who are small, have underlying esophageal disease such as a stricture (e.g., following previous injury such as a caustic ingestion), have a history of esophageal surgery (e.g., tracheoesophageal fistula repair, esophageal atresia repair, or gastric fundoplication), or have ingested multiple coins at one time [59]. Emergent endoscopic removal of esophageal coins should be performed in symptomatic patients unable to swallow their secretions or experiencing acute respiratory symptoms. Asymptomatic patients or those able to handle their secretions can postpone endoscopy for 12–24 h to allow an appropriate preanesthetic fast. If there is significant delay, the radiograph should be repeated immediately before the procedure to establish that the coin has not passed to the stomach. A retrospective radiologic review of 31 pediatric patients with esophageal coin ingestions reported that 9 of the 11 patients who were asymptomatic had passed the coin upon a 24-h follow-up radiography, thereby avoiding a removal procedure [60]. The other 20 patients were symptomatic (or did not return for follow-up), and one required immediate removal for severe symptoms. Glucagon has not been shown to be effective in facilitating esophageal coin passage in children.

Battery ingestions are also especially common among young children. Management of battery ingestion is significantly different from coin ingestion despite their similar size. Symptoms following battery ingestion are uncommon, occurring in only 3–0 % of cases [61], and correlate poorly with clinical outcome. Batteries of any size lodged in the esophagus cause significant morbidity due to its caustic material and possible discharge of current. Therefore, despite the lack of symptoms, every case of suspected battery ingestion warrants immediate radiography to locate the battery. Leakage of its alkaline contents into the esophagus may result in liquefaction necrosis similar to those following caustic ingestion of lye (sodium hydroxide pH >11.5). Very early complications have included esophageal perforation (within 6 h), tracheoesophageal fistula, esophageal stricture or stenosis (within 10 h), and death. Immediate endoscopic removal of esophageal batteries is warranted, despite the increased risk of aspiration in a patient who has not been fasted [58].

Food impaction is the most common cause of accidental "foreign body ingestion" in adolescents and adults. A previous history of food impaction or of feeling that "food gets stuck" is frequent [62]. In approximately 95 % of meat

impaction cases, there are associated underlying esophageal pathology, such as esophageal narrowing from peptic, caustic, or postoperative strictures or stenosis, eosinophilic esophagitis, or motility disorders [58]. If there is a suspected food impaction, a plain radiograph can be obtained. Contrast administration should be avoided to minimize aspiration of contrast that has pooled above the impaction. Patients unable to handle their secretions require urgent endoscopic disimpaction. Symptomatic patients who are able to handle their secretions should undergo endoscopy within 12 h. In no case should "meat tenderizers" be given, as this may lead to hypernatremia and "tenderization" of the esophagus. At endoscopy, removal of the impaction, rather than blind bougienage into the stomach, is desirable because of the high rate of underlying esophageal pathology [58].

Esophageal Motility Abnormalities

Achalasia is characterized by impaired relaxation of the LES in response to swallowing. It is rare in children, with an incidence of 0.11 cases per 100,000 children. The two most common presenting symptoms are vomiting (85 %) and dysphagia (82 %). Vomiting is more frequent in children less than 5 years of age and dysphagia more common in older children. Achalasia is usually progressive, beginning with solids and frequently progressing to dysphagia for both liquids and solids by the time of diagnosis. Other complaints include weight loss (54 %), chest pain (30 %), and cough (24 %) [63]. Achalasia in younger patients is associated with trisomy 21, triple A syndrome (alacrima, achalasia, adrenal insufficiency), and familial dysautonomia [64]. Treatment options include LES dilation with dilators or endoscopic balloon dilation, botulinum toxin injection in the LES for temporary relief of symptoms, or surgical myotomy with or without a partial fundoplication for more permanent relief.

Nonspecific esophageal motility disorders (NEMDs) are present in up to 50 % of adults with noncardiac chest pain or dysphagia. A study of 154 pediatric patients with at least one of the following symptoms (chest pain, dysphagia, or vomiting) showed that the most common disorder was GERD diagnosed by pH studies in 109 children. The remaining 45 (29 %) children underwent manometric evaluation, and 30 were found to have esophageal motor disorders: 12 achalasia, 3 intestinal pseudo-obstruction, 1 diffuse esophageal spasm, and 1 dysmotility following tracheoesophageal fistula (TEF) repair. NEMDs were diagnosed in 13 of the patients and accounted for 8 % of the diagnoses. Esophagitis itself can sometimes cause a disturbance in the normal contractility and is associated with increased transient LES relaxations facilitating reflux episodes which perpetuate the cycle.

Barium esophagram or UGI series is the most useful initial diagnostic test for suspected esophageal motor disorders, including achalasia. The classic radiographic features of achalasia include bird-beak appearance of the GE junction, dilated distal esophagus, retained food material in the esophageal body, and poor stripping waves (peristalsis). The caveat is that the contrast study may be normal in early achalasia. Manometric confirmation of suspected motor disorders of the esophagus is critical as it has an impact on management. Manometry may reveal abnormal esophageal motility in patients with GERD, with typically a decreased number and abnormal esophageal body contractions [65, 66], and in eosinophilic esophagitis [67]. Manometry may be useful in patients with GERD who have failed acid-suppression therapy and have negative endoscopic findings. Antroduodenal manometry is sometimes useful in neurologically handicapped children because generalized foregut dysmotility may mimic reflux and feeding intolerance [68].

Postsurgical Complications

Fundoplication

Fundoplication is performed with the intent to prevent severe gastroesophageal reflux, its associated symptoms, and long-term sequelae. Sometimes surgery may not resolve the symptoms, or new and troublesome symptoms may

arise. Direct side effects from the surgery include dysphagia, which may be related to edema of the gastroesophageal (GE) junction, transient esophageal hypomotility, excessive tightness of the wrap, obstruction from adhesions, hiatal herniation of the wrap, or paraesophageal hernia. Inadvertent vagal nerve injury during surgery or entrapment of the vagus nerve in a tight wrap may also cause a downstream effect on gastric emptying [69]. The fundoplication wrap creates a relatively fixed high pressure zone at the distal esophagus which prevents reflux but may also impede bolus movement through the GE junction into the stomach. In the presence of underlying esophageal hypomotility, a fundoplication may worsen dysphagia due to ineffective bolus clearance.

There is no reliable method to surgically construct an ideal anti-reflux barrier of appropriate tightness in an individual patient. Patients without any apparent esophageal dysmotility may exhibit symptoms of slow esophageal transit time, such as eating more slowly than their siblings, retching, or dysphagia after a fundoplication [70]. Dysphagia is very common in the immediate postoperative period and sometimes may persist up to 6 months or longer after fundoplication. Dysphagia lasting beyond 6 months warrants further evaluation to rule out other causes such as achalasia, eosinophilic esophagitis, or other esophageal pathology.

Failure of fundoplication to improve preoperative symptoms may be due to an incorrect original diagnosis of GERD. There are many conditions that may mimic GER, such as cyclic vomiting, rumination, gastroparesis, eosinophilic esophagitis, or esophageal dysmotility [69]. A fundoplication can do more harm than good in most of these conditions. Post-fundoplication complications are more prevalent in children with neurologic impairment, chronic lung disease, esophageal atresia, or a generalized motility disorder [69]. These children not only have a challenging physiology, but often are unable to accurately express what is bothering them. Therefore, caution must be exercised before giving a diagnosis of GERD and recommending a fundoplication.

Cardiac Surgery

During open cardiac surgery, the vagus nerves running alongside the esophagus may sustain injury from the surgical retractors. This may lead to vocal cord weakness (from damage to the recurrent laryngeal branch), esophageal dysmotility, and poor gastric emptying (gastroparesis). Infants with a history of cardiac surgery often have feeding problems and/or aspiration in the immediate postoperative period and may need nasogastric feeds until recovery of the vagus nerves. The recovery period depends upon the degree of vagal nerve injury and presence of other comorbid conditions, including malnutrition and hypotonia, which may impact oral motor skills, especially in children with Down syndrome.

Esophageal Atresia and Tracheoesophageal Fistula

Surgical treatment of esophageal atresia (EA) with tracheoesophageal fistula (TEF) is a standard procedure with a spectrum of complications, such as GER, tracheomalacia, disordered esophageal peristalsis, and anastomotic esophageal stricture (see Fig. 103.8). In the neonate with EA, motility disorders of the esophagus have been identified even before surgical intervention [71] and are suggestive of a congenital origin. Morphologically, these patients have abnormalities of the Auerbach's plexus in the esophagus and stomach [72]. Surgical dissection and mobilization of the esophagus during EA repair can damage the motor innervation [73]. Postoperative esophageal dysmotility can certainly be explained by a combination of congenital and acquired factors.

Impaired gastric motility has been demonstrated postoperatively in patients with EA-TEF repair. Delayed gastric emptying was prolonged in the EA group compared with the control group [74]. Manometric studies of gastric motility have shown that peristalsis was abnormal in about 45 % of patients after EA-TEF surgery. This impaired motility often manifests itself as symptoms of dysphagia or feeding difficulties. The reported incidence is about 60 %, when considering both daily and occasional symptoms [75].

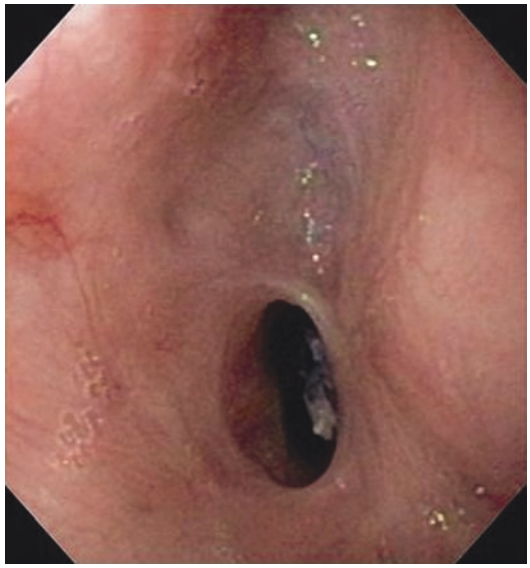


Fig. 103.8 Anastomotic esophageal stricture

Another frequently reported symptom is dyspepsia and is related mainly to GER. Motility disorders have been correlated with the onset of GER, and reflux may be responsible for dysphagia when it leads to esophageal stenosis [74].

Extrinsic Esophageal Compression

Symptoms and physical findings produced by vascular rings are primarily those involving airway or esophageal compression. Most patients with a vascular ring present with symptoms in infancy or early childhood. Signs and symptoms include dysphagia, feeding difficulty, stridor, cyanosis, wheezing, respiratory distress, apnea, a characteristic high-pitched, brassy cough, a history of asthma, or recurrent pneumonia. In some cases, airway symptoms are worsened or aggravated by feedings. Symptoms of airway obstruction predominate in patients who present in infancy or within the first few years of life. Symptoms which manifest soon after birth include slow breast or bottle feeding, fatigue with feeding, frequent regurgitation, or aspiration pneumonia. In most cases, workup is initiated when solid foods are introduced, which causes more pronounced dysphagia.

The association of difficulty in swallowing and an aberrant right subclavian artery is termed *dysphagia lusorum*. Martin et al. described four children who had difficulty swallowing and aberrant right subclavian arteries [76]. Esophageal manometry showed high pulsatile pressure in the area of the aberrant right subclavian artery in each child (12–100 mmHg). Three of the four children underwent surgical correction, and their symptoms resolved. Postoperatively, esophageal manometric findings were normal. The authors concluded that dysphagia lusorum occurs in children, and esophageal manometry shows persistently increased intraesophageal pressure, causing a functional partial obstruction in symptomatic children with dysphagia lusorum.

Conclusion

Food refusal and swallowing disorders may represent symptoms of a wide array of underlying anatomical or functional upper aerodigestive disorders along with a behavioral overlay. It is imperative that the specialist has a detailed understanding of the upper aerodigestive tract, as this will facilitate in choosing the appropriate test and treatment modality. The management of younger children presenting with food refusal tends to be more challenging; and an interdisciplinary approach is felt to be most effective in addressing this issue.

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The Child with Apnoea or ALTE 104

M.T. Rawat

Apnoea, Apparent Life-Threatening Events and Gastro-oesophageal Reflux Disease

The presentation of gastro-oesophageal reflux disease is variable, is dependent on age but can present in a fairly typical manner in most cases. In adults and adolescents, the cardinal symptoms are thought to be those of heartburn (retrosternal burning sensation) and regurgitation.

However, it is also proposed that GERD can manifest itself in an atypical manner in some patients such that organ systems and structures separate to the oesophagus (extra-oesophageal/supra-oesophageal) are involved producing symptoms and signs that are not seen with classical GERD. This chapter will focus on some of these manifestations, primarily apnoea, but also touch on apparent life-threatening events (ALTEs). Recent guidance on gastro-oesophageal reflux and developments in techniques to detect it will be discussed initially, followed by a review of the evidence for links between GER and apnoea including possible pathophysiological mechanisms involved.

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Gastro-oesophageal Reflux Disease: Definitions and Natural History

Defining GER and GERD has been the subject of recent national and international guidelines for both adults (e.g. Montreal classification) [64] as well as children [54, 70]. The summary diagram of the paediatric version of these statements is shown in Fig. 104.1

After a brief discussion of typical oesophageal manifestations of GERD, investigative techniques available and general management in children, the focus will turn to the complex relationship between apnoea and apparent life-threatening events (ALTEs) and GERD, one of the atypical presentations of reflux that have become known as extra-oesophageal and supra-oesophageal reflux.

Extra-oesophageal Reflux

GER is defined as the passage of gastric contents into the oesophagus with or without vomiting. It is stressed that GER itself is a normal physiological event that occurs several times daily in all age groups, is usually short lived (less than 3 min) and occurs mostly in the postprandial period. Regurgitation in paediatrics is defined as the passage of refluxed contents into the pharynx, mouth or from the mouth.

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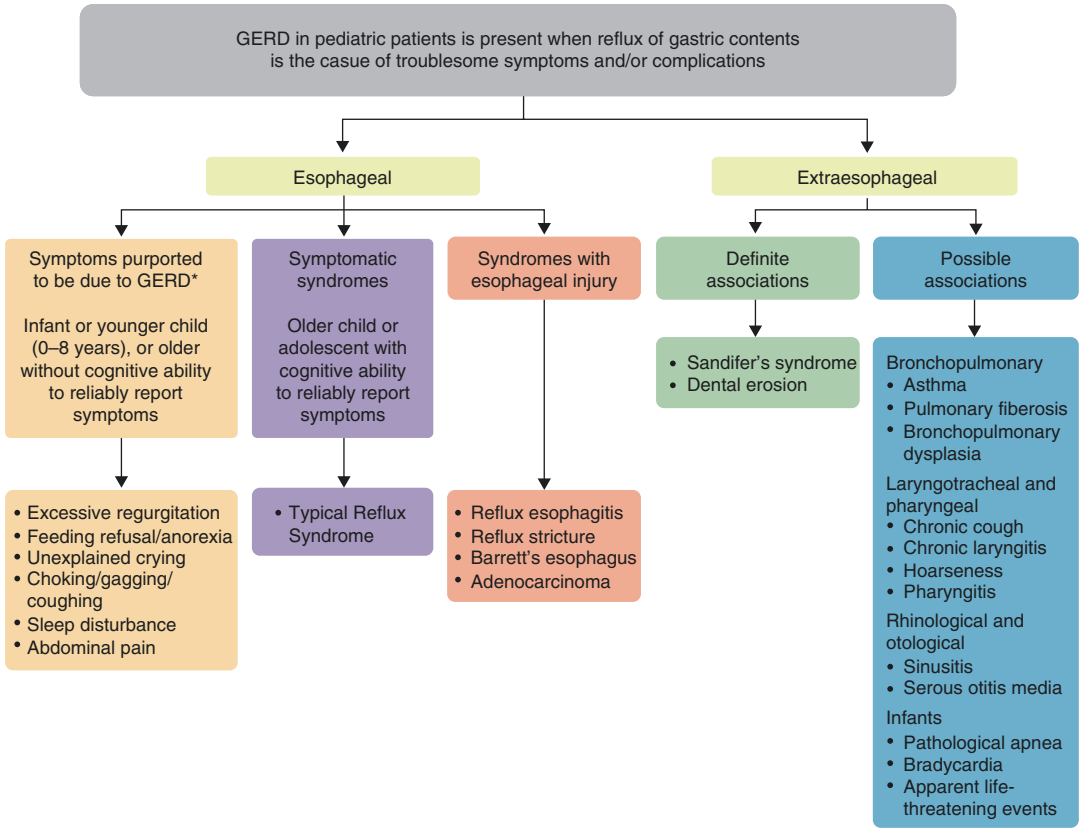

Fig. 104.1 Shows the definition and various manifestations of GERD as in a recent global, evidence-based consensus. Note that apnoea and ALTE are listed as possible associations (From reference [54])

GERD is defined as troublesome symptoms or complications that occur secondary to GER [64].

It is apparent that the diagnosis of GERD has become more patient centred and symptom based.

GERD symptoms vary and are age dependent with adolescents (>12) having similar symptoms to those described by adults, i.e. heartburn with or without regurgitation in the case of typical reflux syndrome.

In children, this definition is used too though some caveats have been recommended. The issue of what is troublesome is complicated in younger patient. Symptom reporting is often dependent on the attentiveness of the parent or main carer particularly in younger age groups or those children without skills to verbalise [4] (e.g. those with neurological impairment). Symptoms should be troublesome to the patient and not just to the carer [54].

Longitudinal studies have shown that GER occurs commonly through infancy with a peak at about 3–4 months of age followed by a decline so that by 14 months less than 5 % of infants are having episodes of regurgitation and by 18 months the numbers affected are negligible [30, 36]. A more recent prospective study that used the Rome 2 Criteria for diagnosis of functional regurgitation in an Italian population showed a lower prevalence (12 %) than previous studies but that it usually resolves by 18 months [7].

Symptoms purported to be due to GERD in infants are nonspecific with regurgitation, irritability, crying, back arching, sleep disturbance and breathing difficulties, food refusal and feeding difficulties being amongst those commonly ascribed to the condition. It can be difficult to differentiate between normal patterns of

regurgitation and crying and troublesome symptoms, and the recent guidelines suggest that a symptom-based diagnosis of GERD in infants is problematic.

Toddlers and pre-school-aged children tend to present with food refusal, regurgitation and abdominal pain, and older children may present with regurgitation or vomiting, cough and epigastric pain or heartburn [18].

To highlight the underappreciated occasional complexity of making a diagnosis of GERD in children, even in adults, the diagnosis can at times be complicated. Accuracy of diagnosis in adults has been questioned recently. The Diamond Study [10], in which a 12-point self-report questionnaire was compared to family doctors and gastroenterologists, showed great accuracy of diagnosis of GERD. In just under half of patients, the main symptoms were those of regurgitation and heartburn, demonstrating the wide spectrum of symptoms that are attributed to GERD in a primary care population of adults.

A condition that could potentially masquerade as GERD in infants is cow's milk protein allergy. It can be the cause of an identical presentation to that of GERD, hence the recommendation that a trial of hydrolysed feed be used when considering the various treatment modalities [66].

Symptom questionnaires have been developed and validated for use in diagnosing GERD. In adults, patient-centred self-assessment questionnaires such as the GERDQ have been developed [22] for use in primary care.

The most thoroughly evaluated such questionnaire for infant symptoms is the Infant Gastroesophageal Reflux Questionnaire Revised (I-GERQ-R) [27]. It is composed of a series of questions from which an I-GERQ-score can be constructed. However, the correlation between results of the questionnaire and findings at endoscopy and histology has been varied between different centres producing perplexing results in clinical trials.

As can be seen, there is a wide spectrum of presentation of GERD in infancy and childhood. Diagnosis is not always straightforward particularly in the younger, non-verbal child.

Pathophysiology of GERD

The oesophagus can usually maintain its preferred empty state by means of upper and lower oesophageal sphincters preventing entry from above and below of unwanted contents (air, noxious refluxate). The LES in particular is relevant to GERD. It acts as a valve preventing backflow of gastric contents into the oesophagus. It is aided in function by the correct anatomical positioning of the oesophagus in relation to the crura of the diaphragm. The intra-abdominal portion of the oesophagus is also angulated such that pressure changes that occur with breathing help to produce a physiological valve effect such that gastric refluxate into the oesophagus is impeded during the normal breathing cycle.

With regards to these barriers, the oesophagus also has clearance mechanisms (secondary peristalsis in response to distension) as well as epithelial defence mechanisms to counter sustained ingress and potentially damaging exposure to acidic fluids [68].

Disturbance of anyone of these can contribute towards damage to the oesophagus.

The underlying pathophysiology of typical GERD involves transient relaxation of the lower oesophageal sphincter known as a TLESR (that is unrelated to swallowing and subsequent oesophageal peristalsis) that permits flow of gastric contents into the oesophagus [25, 68]. This is the mechanism underlying most GER episodes [24, 26] and has been demonstrated in all age groups including preterm infants (Fig. 104.2), thereby refuting the previously held belief of an immature LOS in infants underlying GER in this group [37]. No clear-cut oesophageal motor abnormality has been demonstrated in those with GERD which limits the use of certain techniques such as oesophageal manometry in making a diagnosis (see section below) [65].

Anatomical differences between infants and older children such as a reduced length and straighter (rather than angulated) intra-abdominal portion of the oesophagus, supine positioning, and relatively large volume of feeds (up to 180 ml/kg/day in an infant would equate to 14 L/day in an adult) can explain why infants are naturally predisposed to GER [68].

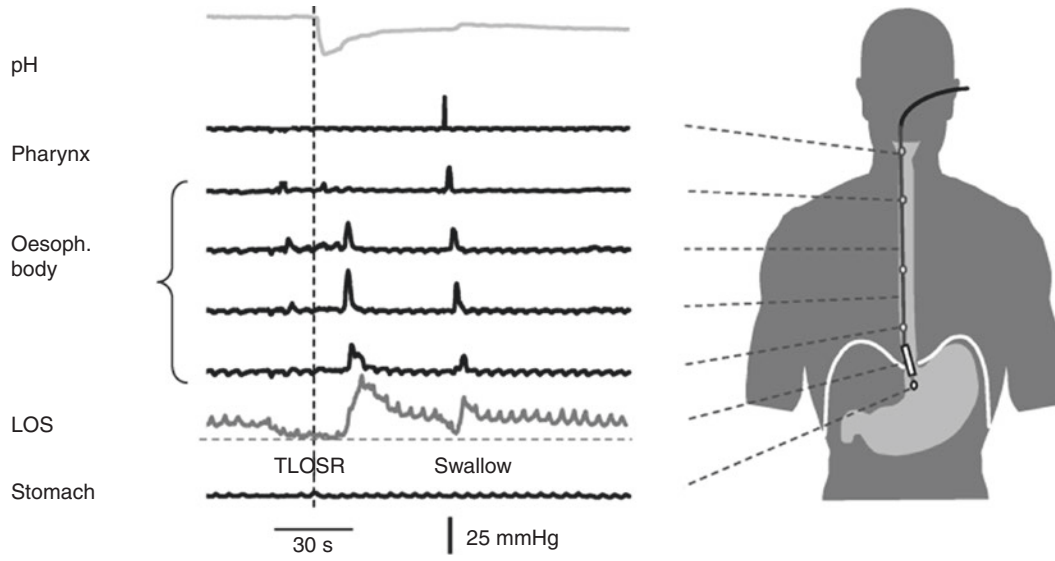

Fig. 104.2 A manometry tracing showing the relationship between a transient lower oesophageal relaxation episode and fall in oesophageal pH measurement, as opposed to a subsequent swallow induced relaxation (From reference [3])

Predisposing Conditions

Certain conditions can predispose patients to severe GER/GERD and its complications. They include underlying neurological impairment secondary to a variety of causes, e.g. cerebral palsy and genetic and chromosomal abnormalities. Chronic respiratory conditions such as cystic fibrosis as well as congenital abnormalities of the oesophagus such as oesophageal atresia or tracheo-oesophageal fistula also contribute to GERD [68, 69].

Otherwise healthy children with hiatus hernia and family history of Barrett's oesophagus also have a higher prevalence of severe GERD and its complications.

Diagnosis and Investigative Techniques

A clinical history can prompt the diagnosis more readily in older children and can be used to look for any warning symptoms and signs indicative of other serious disorders that could be behind a presentation involving crying, irritability, vomiting, poor weight gain and feed refusal in an infant or young child. The range of infections, neurological, cardiac, surgical and gastroenterological conditions that could present in this manner is wide and is well documented in the recent guidelines. The use of questionnaires in the youngest age groups may be of benefit too.

Awareness of other disorders that can mimic features of GERD such as cow's milk protein allergy and eosinophilic oesophagitis is important as treatment is very different [15].

Selected investigations may be useful in the workup of the paediatric patient with GERD as there is no single gold-standard test for GERD.

Contrast studies can confirm that no underlying anatomical abnormality is present but is neither sensitive nor specific enough for diagnosis of GERD as it provides only a snapshot of events at the time of investigation.

Surrogate tests that help to quantify reflux include intra-oesophageal pH monitoring, multichannel intraluminal impedance monitoring and scintigraphy.

Until recently, the 'gold-standard' investigation to assist diagnosing GERD was felt to be the pH study using antimony electrodes on a catheter left in situ in the distal oesophagus to quantify oesophageal acid exposure time [66].

Various parameters can be recorded quantifying or reflecting acid exposure time. It does not however always correlate with symptoms or findings at endoscopy. It is excellent for quantifying acid reflux but not other forms of reflux [39].

The technique can also be used to assess the temporal relationship between reflux events and symptoms, and several methods exist such as the symptom index, symptom sensitivity index and more recently the symptom association probability that expresses the likelihood that the patients' symptoms are related to reflux. It is worth remembering that although the symptom may be found to be associated with reflux, this does not imply causality [6].

However, it has been appreciated for a long time that most reflux that occurs in the postprandial period (particularly in infants) is non-acidic in nature due to the buffering effect of milk feeding and so GERD may be underestimated. Hence, it is difficult to investigate all forms of reflux using a pH-dependent method [37].

pH metry is useful to check on the efficacy of antisecretory therapy in reducing acid exposure time. It is also the monitoring system for which the best clinical data is available that correlates with therapeutic success or failure [47].

Recently the pH study has been supplemented by the technique of measuring intraoesophageal electrical impedance [71, 72]. This technique makes use of an intraluminal catheter with closely spaced electrodes between which the impedance is measured. The latter is similar to electrical resistance as defined by Ohm's law, i.e. the quotient of voltage and electrical current, and depends on the ionic concentration of the luminal contents surrounding the catheter with air having high impedance and liquid low impedance [23, 65]. The principle of the technique is based on a change in electrical impedance during the passage of a bolus through a measuring segment. The use of multiple segments along the catheter along the length of the oesophagus allows for the analysis of the direction of movement of the bolus with a unique pattern being produced with retrograde movement [74] (Fig. 104.3).

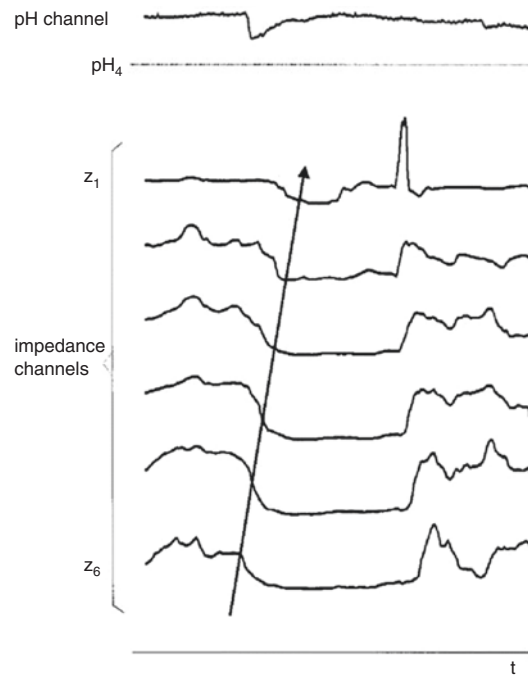

Fig. 104.3 Shows an impedance tracing that demonstrates a drop in impedance in the distal channels (Z6 lowermost tracing)) initially, with a progressive retrograde movement up the catheter to the more proximal channels in mid-upper oesophagus (Z1) with time (*x-axis*), indicating a reflux event of a non-acidic (pH trace not less than 4) nature (From reference [62])

It can be useful in two areas of relevance to reflux: both to aid diagnosis of GERD and in oesophageal function testing.

When impedance monitoring is used in conjunction with pH metry on a combined multichannel catheter, further data can be obtained. This includes qualities such as pH (acid, weakly acid, non-acid) and composition (gas/fluid) of refluxate as well as its direction and the proximal extent of movement, which may be useful when investigating extra-oesophageal symptoms. An example of an impedance tracing showing a non-acid reflux impedance change is illustrated in Fig. 104.3

The technique is sensitive to very small volumes. Temporal associations and relationship of symptoms to reflux can be analysed. Another advantage is that the technique can be used on patients whilst 'on' therapy as it can detect fluid movement independent of pH [5, 6].

Again using the technique in conjunction with polysomnography (sleep studies) has been useful in looking at the temporal relationship between reflux events and postulated atypical or extra-oesophageal symptoms of reflux such as apnoea, ALTE and cough [37].

Oesophageal motility is well studied in adults but data is still lacking in children. A consequence of oesophageal dysmotility may be GERD yet patients with normal motility can experience severe GERD symptoms. Oesophageal manometry can be useful in siting probes close to the lower oesophageal sphincter or diagnosing underlying oesophageal motility disorders rather than diagnosing GERD itself.

The use of MII (impedance testing) together with oesophageal manometry is another area that has been developing recently since the advent of the impedance technique and gives information about the relationship between oesophageal pressures and bolus flow that reflects oesophageal function, for example, bolus clearance, and avoids the use of ionising radiation [65].

Other studies that may be of use include nuclear scintigraphy that can detect reflux as well as complications such as aspiration but can also estimate gastric emptying time.

Management of GERD

The management of GERD in childhood varies with age. In the youngest patient group (infants), conservative measures are initiated and include positional changes at feed times, as well as changes in manner of feeding with thickening of feed, alteration of volume and frequency of feeds and a trial of alternative milks such as hydrolysed formula as cow's milk protein intolerance may be an underlying cause of symptoms identical to those of GERD.

In the older child, altering the volume of intake (avoiding large meals) as well as trigger foods and avoidance of other environmental factors such as cigarettes smoke can be incorporated into the management plan.

Medications such as prokinetics, histamine receptor antagonists, proton pump inhibitors amongst other agents can be used. The data for the effectiveness of most of these agents is limited in children, but documented healing of the uncommon finding of erosive oesophagitis attributed to GERD has been found in those on PPI treatment. This topic is covered in greater detail in recent reviews and guidelines [70] as well as in other areas of this book.

Extra-oesophageal/Supra-oesophageal Reflux

Over the last 25 years, there has been accumulating data to support links between GERD and illnesses and symptoms arising in other organs and structures beside the oesophagus. These are known as extra- or supra-oesophageal reflux syndromes [46, 49, 50].

The respiratory tract – both upper and lower airways – the mouth and the otorhinolaryngological structures are mainly implicated [67]. Studies have shown that up to a third of adults may have some extra-oesophageal symptoms (EES).

It has been postulated for some time that direct contact of acid with respiratory mucosa can result in ulceration as found by Cherry et al. [8] who found improvement of laryngeal ulcers in patients with GERD as demonstrated on barium studies when treated for reflux. Experimentally induced granuloma formation on the true vocal folds in dogs occurred after exposure to gastric juice [9].

Chronic cough, reactive airway disease (asthma), apnoea (of prematurity), bronchopulmonary dysplasia, recurrent pneumonia, subglottic stenosis, laryngitis, hoarseness, laryngopharyngeal reflux, sinusitis, middle ear disorders and dental erosions [11, 12, 14–17, 29, 46, 48, 51, 53, 59] are to name but a few of the disorders proposed to have a link with GERD. Some of these are outlined in Fig. 104.1.

The Montreal definition of GERD in adults [64] described several established extra-oesophageal symptoms associated with GERD. These included cough, laryngitis, asthma and dental erosions. There were also several other disorders that are proposed to have an

association with GERD: sinusitis, pharyngitis, recurrent otitis media and idiopathic pulmonary fibrosis.

Before assuming causality, there should be both epidemiological and temporal association between GERD and the symptom/syndrome in question as well as a feasible pathophysiological concept underlying the link. Treatment of GERD should then result in improvement or elimination of the extra-oesophageal symptoms [28].

The commentary on the statements dealing with extra-oesophageal syndromes emphasised that though the volume of literature dealing with the subject is large, the strength of studies is relatively weak such that a causal link could not be guaranteed with certainty.

In the development of the Montreal statements [64] regarding GERD in adults, it became clear that:

1. The link between GERD and the EES is more likely to be an association rather than a causal relationship as was initially thought to be the case during the development of the statements.
2. It is rare for the EES to present alone without any manifestation of more typical GERD presentations.
3. The conditions involved are likely to have a multifactorial pathogenesis and that GERD is one of the several aggravating factors.
4. The data supporting a beneficial effect of reflux treatments for extra-oesophageal symptoms is weak.

In contrast to GERD in adults where there is more prevalence data available (up to a third of adults with GERD may have EES), there is less data in paediatric patients.

It is easy to understand how diagnostic challenges can arise in infants and children with non-specific (e.g. irritability and apnoea) or extra-oesophageal symptoms such as chronic cough and wheeze/asthma.

A case-control study conducted in Texas looked at the association between GERD and several extra-oesophageal manifestations of GERD in 1980 children older than 2 without neurological deficits or congenital oesophageal abnormalities. Within this cohort, a substantial proportion (one third) had other recognised predisposing factors to GERD such as cystic fibrosis, severe obesity or scleroderma. A significant statistical association between laryngitis, sinusitis, asthma, pneumonia and GERD was found [11, 19–21].

A recent systematic review looked into the prevalence of extra-oesophageal symptoms in children with GERD or the prevalence of GERD in those with extra-oesophageal symptoms as well as the size of the association between the two. A range of symptoms was studied, particularly those highlighted in the Montreal and paediatric definitions of GERD. It concluded that there may be an association between GERD and asthma and possible associations between GERD and a variety of conditions including pneumonia, bronchiectasis, acute life-threatening events (ALTEs), laryngotracheitis and sinusitis [63].

The focus now turns to apnoea and the possible relationship to GERD.

GERD and Apnoea/Apparent Life-Threatening Event (ALTE)

As is apparent from the preceding discussion, GER is a common finding in infancy. It has been proposed to be the cause of several other disorders including apnoea and apparent life-threatening events (ALTEs), which themselves have been implicated in the pathophysiology of the sudden infant death syndrome (SIDS). It is useful to define these disorders in detail according to commonly accepted definitions and then to discuss the anatomical and physiological relationships between the structures involved as this will then ease understanding of the proposed pathophysiological mechanisms underlying any possible links between GERD and apnoea.

Definitions

GER and GERD are defined in previous sections.

Apnoea is usually defined as cessation of breathing for 20 s or for any length of time if accompanied by change in colour, muscle tone or heart rate for a period of time.

ALTE is defined by a National Institute of Health consensus conference as an episode that is frightening to the observer and is composed of a combination of apnoea, a change in colour (usually cyanotic or pallor, but sometimes erythematous/plethoric), muscle tone (mostly limpness), choking or gagging, which requires intervention by a caregiver [35]. After an ALTE, an infant can appear well with no obvious features of illness, and even after a thorough assessment, only 50% of patients will have a diagnosis [52].

Apnoea of infancy occurs in those infants with a gestational age of 37 weeks or more at the onset of apnoea, whilst apnoea of prematurity is defined as the sudden cessation of breathing that lasts for 20 s or is accompanied by bradycardia or oxygen desaturation (cyanosis) in an infant younger than 37 weeks of gestational age [35].

SIDS is defined as the sudden death of an infant under 1 year of age that remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene and review of the clinical history. Since the early 1970s, it has been proposed that apnoea may be the pathophysiological precursor to SIDS, and so home cardiorespiratory monitoring proving this link has never been forthcoming despite intense research [35, 46]

Both apnoea, ALTE and SIDS have a wide variety of possible causes, but all have been associated with GERD. A recent systematic review to determine the causes of ALTE in infants found that the most common diagnoses included GER (the major cause), seizure, lower respiratory tract infection and other unknown causes. The diagnosis of GERD was made using a variety of investigative techniques including pH metry, barium studies, manometry and milk scans in various combinations or solely on clinical grounds in some cases. It was the only diagnosis that appeared in every study analysed [31].

The fact that all occur in the same age range and can occur during sleep or wakefulness lends itself to how one may seemingly imply causality between GERD and these events [40]. However, this relationship is complex and has often been based on circumstantial evidence. Often causality is proposed, yet the literature shows conflicting results and is inconclusive and even shows that there may not even be an association between them.

Upper Airways and Oesophagus

That there is a presumed relationship between apnoea and GERD is unsurprising given the close proximity of the oesophagus to the upper airways. The upper aerodigestive tract consists of the nose, mouth, pharynx, larynx and upper oesophagus and deals with the passage of air and food. A complex neuromuscular apparatus together with fine coordination of its various parts is necessary for normal swallowing, breathing and respiratory control to occur.

The pharynx and oesophagus are both derived embryologically from the foregut, and the development of the oesophagus is discussed in earlier chapters. In normal (nutritive) swallowing that consists of four phases (oral preparatory, oral, pharyngeal and oesophageal), it is the coordination between events during the latter two phases that is of concern when considering the pathophysiology of apnoea and possible links to GERD.

Protection of the airway to prevent ingress of either fluid (amniotic fluid in the foetus, milk/water in the infant) or food is essential during the process of swallowing. This is facilitated by closure of the glottis (laryngeal closure), whilst the bolus of fluid or food passes between the pharynges, propelled by contraction of pharyngeal constrictor muscles, through the relaxed upper oesophageal sphincter into the proximal portion of the oesophagus. The larynx's primary function is to act as a sphincter providing protection to the lower airways from invasion by fluid. This begins in utero, preventing contact between amniotic fluids that is chloride poor and contains potentially noxious substances to the lungs in contrast to the chloride-rich fluid produced by the respiratory epithelium [41, 42, 44].

Swallowing can be either nutritive, essential for food intake and growth or nonnutritive that functions as a means to clear secretions, saliva or gastric refluxate from the pharynx and oesophagus. Nonnutritive swallowing (NNS) begins in the pharynx with the pharyngeal phase and is triggered by messages in the afferent limbs of the reflexes alluded to above [45].

One can see from the above description that there is a need for a physiological apnoea of short duration to occur during the act of nutritive swallowing in order to protect the lower airways.

Pathological apnoea however is more prolonged and is detrimental to the well being of the infant. It is traditionally divided into obstructive or as central dependent on the presence or absence of respiratory effort or as mixed when a combination of the two occurs.

Apnoea of prematurity has been the focus of intense research over several decades, and insights into its pathophysiology have emerged. Premature infants have immature respiratory control patterns with impaired ventilatory responses to hypoxia, hypercapnia and an exaggerated inhibitory response to stimulation of airway receptors [1].

Given the crucial nature of the processes of breathing and swallowing, the interaction between the two is closely controlled. This involves complex neural circuitry and reflexes with afferent limbs using the superior laryngeal nerves, nucleus of the tractus solitarius and second-order neurons, medullary control centres and efferent vagal limbs. These reflexes, the laryngeal chemoreflexes, have been studied in great detail by various groups of researchers and may underpin any potential link between GER events and apnoea [60].

Observations that apnoea often occurs during or after a meal/feed suggest a relationship, yet it is known that this is the time during which GER is most common. Some preterm infants, particularly those with bronchopulmonary dysplasia (also proposed to be associated/caused by GERD by some), develop marked hypoxemia during bottle-feeds.

Several mechanisms have been proposed including immature coordination between suck, swallow and breathing, activation of the laryngeal chemoreflexes, GER, diaphragmatic fatigue or a combination of these [43].

Proposed Pathophysiology Linking GER and Apnoea: Laryngeal Chemoreflexes

Looking at apnoea of prematurity in a critical manner, a recent review found that despite uncertain evidence, premature infants frequently undergo evaluation for reflux and antireflux medications are amongst the most highly prescribed medications in neonatal care, with a significant number of infants discharged on them.

A variety of reflexes can be postulated to link GER and apnoea and include oesophago-glottic closure reflex (oesophageal distension stimulates glottis closure), aryepiglottic closure reflex (misdirected fluid at the posterior margins of the glottis) and laryngeal chemoreceptor reflexes. An afferent limb could be stimulated in any of these areas (oesophagus, upper airway) leading to a common efferent response culminating in glottis closure and obstructive apnoea [56].

Thach has described some of the evidence that has accumulated for laryngeal chemoreflexes and their role in apnoea [60, 61]. It was established that at times of regurgitation of gastric content, the upper airway is protected by reflex behaviour that included anatomical closure of the airway at or above the level of the larynx. There then followed the initiation of swallowing once the bolus of refluxate was in the pharynx, serving to clear the pharyngeal area of potentially damaging material. In some groups of infants, the respiratory pause could be prolonged [33] with repeated swallowing and attempted efforts at breathing being common. Bradycardia also occurred at this time, i.e. pathological apnoea. In this same study, prolonged apnoea was also found to occur at times when pharyngeal pH was unaltered implying no acid reflux to the level of the pharynx and no obvious regurgitation associated with apnoeas. Similar responses were found to fluid infused into the pharyngeal area of sleeping infants via a catheter

that was capable of recording swallows. There then followed swallowing and apnoea with occasional cough. Water was more potent than saline at triggering the response, implying ability to distinguish chemical content of fluid.

It also became apparent that once a volume threshold had been reached, the fluid then flowed out of the pyriform recesses and came into contact with the laryngeal mucosa in the inter-arytenoid space, an entrance point to the larynx (see Fig. 104.4). This area is known to be densely populated with chemoreceptor nerve endings that would act as part of the afferent limb of a reflex [60].

The laryngeal chemoreflexes (LCRs) described are triggered by the contact between liquids (both water-/chloride-poor and acidic solutions) and laryngeal mucosal receptors. The LCR also appears to change with maturation of the infant/animal. Immature responses include laryngospasm, apnoea, oxygen desaturation and bradycardia mediated by a vagal efferent limb as well as a redistribution of blood flow to vital organs and hypertension mediated by a sympathetic efferent limb. An older more mature mammal will respond with arousal and coughing rather than apnoea and swallowing in an attempt to protect the lower airways [61].

The presence of various fluids in the upper airways (either feed/gastric refluxate/water) appears to trigger the LCR and apnoea. The activation of receptors in the laryngeal mucosa is the initial step in the process. Laryngeal taste buds, found in high numbers in the area, are thought to be involved. Other receptors have also been described. Receptors in the laryngeal mucosa have been identified for water and respond to low chloride or hypo-osmolar solutions. Laryngeal c-fibres with vanilloid receptors (TRPV1) that are responsive to changes in acidity are found in adult rats. The precise roles of these receptors in the LCR is not yet fully known but potentially may offer future targets for new therapeutic agents [45].

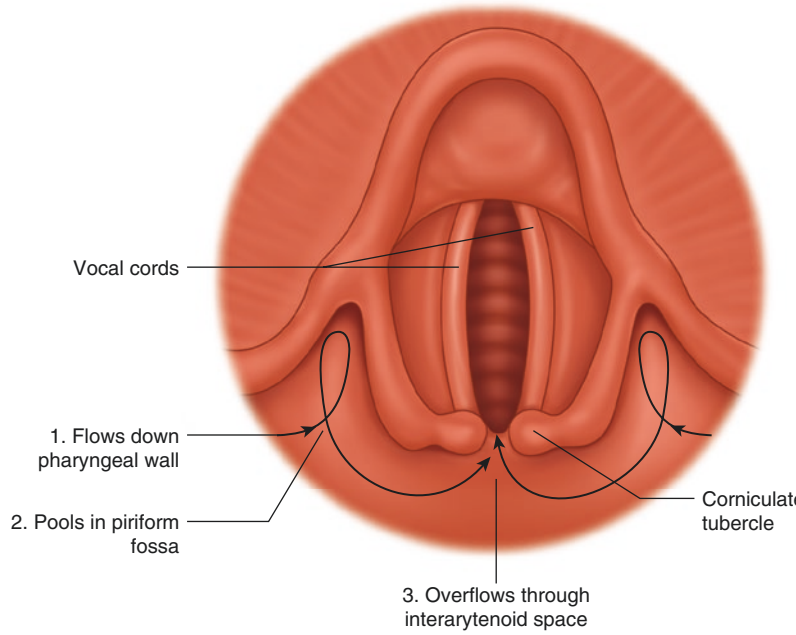

Fig. 104.4 Shows the flow of experimentally placed saline from the pharynx, with pooling in the pyriform fossae, and overspill into the inter-arytenoid space where there is a high density of chemoreceptors at the entrance into the larynx (From reference [60])

The Association Between GER and Apnoea

There have been many studies looking into the relationship between GER events and apnoea given the possibility of a cause and effect relationship between the two that has been discussed above and that could be putatively explained by the mechanisms alluded to in the previous section.

In a study using a combination of pH metry and polysomnography in infants being evaluated after presentation for ALTE in which other causes had been excluded, 21 infants from an initial group of 67 were found to have GER. A group with severe prolonged GER was excluded as the association between the two could not be evaluated. A total of 741 apneic episodes were measured, of which only 140 (19 %) were coupled with GER. Those with GER (pH <4) and those with apnoea (defined as cessation of breathing for at least 6 s or more) associated within 60 s of one another were classified as a coupled event. The majority had apnoea preceding GER, and only in 6.4 % did GER precede the apnoea. The authors concluded that in terms of a cause-effect relationship, the results supported the probability of apnoea as the primary factor with GER secondary to the apnoea. Presumably, the GER is caused by a rise in intra-abdominal pressure associated with the apnoea [2].

As pointed out earlier, apnoea will often occur soon after a feed, the period when GERD is also most likely to occur. Given that recurrent vomiting is a common finding in infants, one may not be surprised that apnoea/ALTE and GER occur together purely coincidentally, such that an association may be present yet causality is not proven. This is a recurrent theme when discussing extra-oesophageal symptoms and GER.

Animal studies show a central or obstructive apnoeic response to infusion of fluid into the oesophagus of a sleeping animal. The apnoeic episode is followed by swallowing and clearance of the bolus [32].

Other studies show acidic GER inducing oxygen desaturation in infants admitted to hospital with an ALTE [13]. Methodological differences between studies (including definitions of apnoea) can make the data hard to compare.

From the data above, it has been postulated that acidic reflux stimulates laryngopharyngeal receptors causing laryngospasm and apnoea. It also appears that only certain episodes of apnoea may be triggered by GERD, such as 'awake apnoea' within 1 h of feeding [57].

Studies using the impedance technique [55] described earlier show an association between 30 % of apnoeic episodes and GER and 70 % of the episodes which reached the pharynx, but only a small proportion of which were acidic in nature [58, 73]. This indicates a role for non-acid reflux in the pathophysiology of these presentations and that would be missed if conventional pH metry were to be used.

More recent studies using the same impedance technique have not supported an association between reflux and apnoea of prematurity [34, 38]; again there are methodological differences between studies. The study by Mousa and colleagues [34] showed little evidence for the association between apnoea and total reflux, acid or non-acid reflux in infants with ALTE or apnoea.

What seems to be more evident from the literature is that the majority of reflux episodes do not cause apnoea and that reflux is not the initiating event. In most studies, there are variable definitions of events, methodology is varied, and the use of older techniques such as pH metry as opposed to the more recently available impedance technique will almost certainly underestimate the role of non-acid reflux in these cases.

As Slocum et al. suggest in their critical review of the subject, one could interpret several of these studies as proving no such link exists. Alternatively, apnoea could occur under certain circumstances in subsets of patients. The proximal extent of reflux or the nature of the refluxate could dictate the response that occurs, and the effect of varying degrees of developmental maturity of different body systems could impact upon the likelihood of the infant being susceptible to GER-induced apnoea [56].

In summary, there may be an association between GERD and physiological apnoea and ALTE; however, a cause and effect relationship

between GERD and pathological apnoea/ALTE has not been conclusively demonstrated. The majority of apneic events do not seem to be caused by GER, yet some reflux may cause some apnoea in certain groups of predisposed patients. Putative mechanisms exist for a link between reflux and apnoea in the form of various reflexes discussed earlier. Studies with similar methodology and definitions are needed in the future to further clarify this controversial area.

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Children with Pulmonary Disorders

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Mark L. Everard and Kostas Priftis

Introduction

The upper gastrointestinal tract and the airways are closely related both anatomically and embryologically. It is therefore not surprising that an abnormality of the normal process of dealing with ingested food substances and liquids may impact on the lungs. For certain conditions such as neurological disorders leading to impaired coordination of the normal swallowing mechanisms or an anatomical abnormality such as a laryngeal cleft which may lead to aspiration of significant quantities of fluid and food material, there is little doubt that there is a causal relationship between the primary condition and the observed pulmonary consequence. At the other end of the spectrum, apparent associations such GER and cough or 'difficult' asthma generate considerable debate as to whether there is simply coexistence of two common conditions or whether there is a causal relationship in one direction or the other. Strong views are often expressed regarding the likelihood of causality despite the absence of convincing data. In large part, these areas of controversies are due to the difficulties of investigating the nature of inflammation within the lower airways, difficulties in clearly identifying aspiration with various imaging modalities and the paucity of well-designed intervention studies. Moreover, the lack of clarity in the use of terms such as 'asthma' compounds the situation.

Children with significant disorders of the oesophagus may present directly to gastroenterologists who may become aware that the child has ongoing respiratory symptoms that may or may not be related to problems in the upper gastrointestinal tract. Similarly the focus of concern may initial focus on respiratory symptoms with the respiratory physician raising concerns that structural or functional problems affecting the upper GI tract are contributing significantly to the pulmonary problems.

Structural problems such as laryngeal clefts and tracheo-oesophageal fistulas will not be discussed further though it should be noted that minor clefts and H fistulae can be very difficult to identify at times even when suspected. The subject of apnoea and acute life-threatening episodes, which if dealt with by a specialist is predominantly dealt with by respiratory physicians, has also been covered in a separate chapter. Therefore, the focus of this chapter will be on the possible adverse effects of GER on the respiratory tract.

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Potential Impact of GER on the Respiratory Tract

The enthusiasm for attributing a range or respiratory problems to GER varies widely between and within countries. The wide range of views and practice reflects, in part, the limited evidence base on which to base practice and the tendency for symptoms to vary over time which accounts for a proportion of perceived 'positive' responses to an intervention. Interventions are generally added when symptoms are most troublesome and the natural tendency for many to spontaneously recover over time will lead to perceived positive responses due to 'regress to the mean'. Problems which are frequently attributed to GER include aspiration, chronic cough, 'difficult asthma' and 'recurrent chest infections'.

GER with Aspiration

A variety of conditions place patients at increased risk of aspiration including structural problems such as laryngeal and palatal clefts, tracheo-oesophageal fistulae and mechanical factors such as endotracheal and tracheostomy tubes.

The group of ambulatory patients in whom there is the most robust evidence and the highest prevalence of respiratory problems attributable to GER are those with cerebral palsy and other forms of neuromuscular disease. GER appears to be significantly more common in this patient group compared with the general population, and its potential for inducing pulmonary problems is greatly potentiated by any associated impairment of reflex protective mechanisms designed to protect the airway from aspiration of food and liquid [1, 24, 34, 38]. GER to the laryngeal inlet places such these individuals as risk of both massive life-threatening episodes and, more commonly, chronic pulmonary aspiration.

It has been suggested that in patients with conditions such as cerebral palsy, GER without swallowing dysfunction is not associated with a significant increase in lower respiratory tract infections but even mild GER is associated with such infections in the presence of swallowing dysfunction [34]. Hence, if aspiration is suspected, much of the diagnostic effort is focused on assessing swallowing and excluding structural problems with and assessment of the presence of GER being only one aspect of the pulmonologists assessment [5, 14, 16].

Other patient groups in whom GER with aspiration appears to have a detrimental effect on outcomes include ventilated preterm neonates in whom aspiration appears to be common and to be associated with a less favourable outcome [22, 23]. However, there are no intervention studies in this population. There are concerns that chest physiotherapy may increase reflux and potentially contribute to aspiration in infants with cystic fibrosis [4, 8] though again no intervention studies have been undertaken.

Pulmonary Consequences of Aspiration

The clinical manifestations of aspiration vary considerably depending on the quantity, frequency and composition of the aspirated material. At the most severe end of the spectrum, children can aspirate significant quantities of material during a substantial reflux event or vomit leading to acute aspiration pneumonitis that may be life-threatening. More typically, aspiration secondary to GER is less intense with relatively small quantities of gastric content being aspirated intermittently. This generally leads to more chronic respiratory symptoms. Cough may not be perceived as a major symptom particularly as the cough reflex may be significantly reduced in children with neuromuscular problems resulting in 'silent' aspiration. The manifestations of these events may be:

1. A persistent/recurrent cough
2. Recurrent 'chest infections'
3. Life-threatening bronchopneumonia

The role of GER reflux in the causation of a persistent cough is the cause of much debate. It is probable that most children who aspirate following GER to the laryngeal inlet develop a recurrent/

persistent cough. However, the role of GER in the causation of a recurrent/persistent cough in the absence of aspiration is much less clear and will be discussed below.

For those with GER who are also aspirating material originating from below the oesophagus, the pattern of respiratory symptoms will vary depending on whether there is a primary irritation of the airways due to a chemical bronchitis/pneumonitis [2, 17, 35] immediately after aspiration or ongoing inflammation due to frequent exposure to chemicals in those with frequent aspiration and/or the presence of a secondary bacterial bronchitis [12, 32]. Aspiration of gastric contents will of itself cause irritation within the conducting airways that is likely to induce coughing which is likely to be related closely in time to the event. However, if the impaired mucociliary clearance together with aspiration of organisms from the upper airways leads to the development of chronic bacterial bronchitis [12], the coughing may be largely unrelated to individual aspiration events. Indeed, with a secondary bacterial bronchitis, the primary insult, GER with aspiration, may have resolved prior to the referral for ongoing respiratory symptoms. This secondary pathology effect might explain some of the difficulty in establishing a correlation between coughing and reflux with aspiration events. The organisms responsible are most commonly the pathogens that frequently colonise the upper airway in childhood notably non-typable *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Moraxella* [12, 19]. This condition has been largely neglected for the past few decades, and it is likely that in large part, this has been due to high levels of antibiotic prescribing in young children. However, with the well-intentioned drive to reduce antibiotic prescribing, the condition is becoming far more prevalent. In previously healthy children, the commonest initiating event appears to be a viral lower respiratory tract infection which leads to impaired mucocillary clearance. Aspiration of secretions from the upper airways in those with a neuromuscular problem may well enhance the likelihood of these respiratory pathogens [exactly the same organisms noted in acute and chronic otitis media] reaching the lower airways and establishing biofilms in the conducting airways.

As noted above, a single large aspiration may precipitate a pneumonitis with possible superadded bacterial infection; it seems very likely that the most common cause for recurrent 'chest infections' in those with neuromuscular problems is a true bronchopneumonia. It is often forgotten that the lungs are compartmentalised into the conducting airways [generation 1–16] responsible for conducting air to and from the transitional and respiratory zone [generations 17–23]. A bronchopneumonia represents a pneumonic illness [infection in the respiratory zone] that has its origins in the conducting airways. The organisms noted above behave quite differently under different conditions. In steady state, in the conducting airways, they probably establish biofilms [40] replicating slowly and inducing chronic but ineffectual inflammatory response. Indeed these organisms use material from neutrophils as part of the complex biofilm structure. During exacerbations, they release significantly greater numbers of planktonic forms with the aim of extending their area of colonisation, and if replication takes off in the respiratory zone, this become evident on the chest X-ray as patchy consolidation and labelled 'pneumonia'. Between exacerbations, the CXR may vary from minor bronchial wall thickening with a generally scruffy appearance to persistent areas of opacification due to failure to clear a region effectively. Ultimately the chronic inflammation associated with the persistence of biofilms can lead to 'bronchiectasis' – a radiological sign than a diagnosis identified by CT scans. As such the development of bronchiectasis in many cases represents a failure of medical management due to a lack of appreciation of the importance of chronic bacterial bronchitis and the natural history of the condition. Hence, the opportunity to intervene at an early stage and prevent progression to changes evident on the CT scan is missed. In those with neuromuscular disease and aspiration, it is not sufficient to simply minimise aspiration or eradicate infection – both must be addressed in parallel.

Trying to preserve a healthy airway in a child with neuromuscular disease has major benefits

for the child, the family and the health-care system as admissions due to 'recurrent chest infections' can be prevented. As noted above, this involves both trying to prevent aspiration and treating bacterial bronchitis in order to prevent the recurrent bronchopneumonias and pulmonary damage often observed in these patients.

Investigation of GER with Possible Aspiration

The presence of recurrent of persistent respiratory symptoms in a patient with known neuromuscular disease raises the possibility of aspiration. This may also be amongst the possible factors in an otherwise 'normal' infant with 'recurrent chest infections' or persistent problems such as chronic cough though it is less likely. Amongst 'normal' infants, a history suggestive of aspiration is more likely to be due to rare structural anomalies such as laryngeal clefts or 'H fistulae' or rare neurological problems affecting oropharyngeal co-ordination such as Moebius syndrome.

Centres are increasingly developing multidisciplinary teams to address the many aspects of investigation and treatment. Investigations may include assessment of swallowing attempting to identify swallowing dysfunction which places a child with GER at greater risk of aspiration, investigations such as pH probes with and without multichannel intraluminal impedance monitoring [18, 37, 44] attempting to assess the degree of acidic and non-acidic reflux and attempts to link reflux with aspiration using bronchoalveolar lavage, gastro-oesophageal scintigraphy and barium esophagrams.

Assessment of Swallowing

Videofluoroscopic Swallowing Study [VFSS] and Fibre-Optic Endoscopic Evaluation of Swallowing [FEES]

A videofluoroscopy undertaken with a speak and language therapist or other trained individuals may identify problems with the swallowing mechanisms and occasionally identify aspiration during swallowing. Such a result would suggest that the subject would be at risk of aspiration from GER should this be sufficient to reach the laryngeal inlet. While invaluable in many, this is a relatively labour-intensive form of assessment involving ionising radiation. While a positive result is highly specific, a negative result does not exclude aspiration. Moreover, *inter*subject variation in interpretation is a potential problem. FEES can be complimentary with similar problems in terms of intra-observe variability, expense and limitation in time of assessment [5].

Bronchoscopy

A combination of probable reflux and possible aspiration would in many centres prompt dual procedures with both upper GI endoscopy and bronchoscopy. The purpose of the bronchoscopy is to try and help confirm or refute the presumptive diagnosis of aspiration and to determine whether there are other factors which may be contributing to the pulmonary symptoms.

Determining whether aspiration has taken place is difficult. Occasionally foreign bodies in the form of solid pieces of food may be found, but this is uncommon. More commonly, there is evidence of inflammation with oedematous and collapsible bronchi. This may be due to aspiration or may be due to bacterial bronchitis, and the visual appearance alone is not helpful. Bronchoalveolar lavage samples are routinely sent for microscopy with the lipid-laden macrophage index [LLMI] being the traditional putative marker of aspiration. However, after early enthusiasm, few would place any reliance of this marker alone as elevated levels can be seen in pulmonary disease without any evidence of aspiration and 'normal levels' being observed in children known to aspirate [9, 26, 29, 30]. It is probable that raised LLMI levels in these cases may be due to inflammation due to other causes such as bacterial bronchitis with the lipid membrane of necrotic inflammatory cells being taken up by macrophages, while levels could be low in an older child in whom fluid is generally in the form of water or juice.

It has been proposed that pepsin [22, 23, 31, 41] is a much more discriminatory marker of

aspiration of gastric contents though this has not been taken up widely due to the lack of commercially available assay, but this appears to be changing. Studies have indicated that pepsin may be detected in samples with a normal LLMI while pepsin does not appear in the lungs of 'healthy controls'. Hopes that measuring pepsin in induced sputum may be a noninvasive means of identifying aspiration proved unfounded as it appears that inducing coughing also induces reflux with pepsin being found in induced sputum samples from 'healthy controls' [20].

In addition to attempting to confirm that aspiration is an ongoing problem, the bronchoscopist will also be seeking evidence of either an underlying structural problem or additional/alternative pathologies. In general, fibre-optic bronchoscopy is believed to be less reliable than rigid bronchoscopy in identifying both a laryngeal cleft and tracheo-oesophageal fistulae in large part due to the angle of approach, but certainly the diagnosis of both is made using flexible bronchoscopes and has been missed using rigid scopes. Tracheomalacia/tracheobronchomalacia is both a risk factor for bacterial bronchitis due to impaired mucociliary clearance and will amplify other causes of cough. Identification of this may modify the physiotherapy used.

Contrast Studies and Milk Scintigraphy

Barium swallow and esophagrams again have a relatively low sensitivity but are probably better at identifying aspiration than milk scintigraphy [3] even though the latter potentially has the advantage of being more 'physiological'. It has been suggested that a milk scintigram performed overnight may be more valuable and sensitive [36].

Management of Chronic Aspiration and Its Consequences

In those with neuromuscular disease who are aspirating material regularly with significant impact on the lower airways, a variety of strategies are available. Having confirmed aspiration, it is clearly important to minimise ongoing aspiration to protect the lower airway. Options include limiting oral feeds to those that are perceived to be relatively safe after careful assessment by speech and language specialists or eliminating feeds all together through the use of nasogastic or, in some, nasojejunal tubes [46] though increasingly commonly gastrostomy tubes are sited. Debate continues to surround the use of surgical intervention fundoplication in those with having a gastrostomy inserted for feeding in those with proven aspiration, some arguing that the majority of patients should have a fundoplication to minimise the risk of reflux while others argue that clear evidence of reflux is required before proceeding to a procedure that has a level of associated morbidity [7, 27]. Addressing the issue of salivary aspiration may also be important even when oral feeds are eliminated.

Identification of bacterial bronchitis is challenging and ultimately may require a bronchoscopy. Eradicating biofilms from the conducting airways is much more difficult than treating a pneumonic episode requiring high doses of antibiotics often for prolonged periods. Physiotherapy to aid clearance is clearly an important component but not sufficient on its own.

It is important to realise that other conditions such as asthma may present with a chronic cough in those with cerebral palsy. Being immobile means that wheeze and overt shortness of breath are rarely observed. The exacerbations associated with viral infections are often termed 'chest infections' and treated with antibiotics. The natural tendency for regression to the mean – the natural improvement that occurs in the days and weeks after an exacerbation – can persuade the clinician that the antibiotics provided for the 'chest infection' is responsible for the perceived improvement. Therefore, clinicians should not lose sight of the fact that asthma will be a factor in the respiratory problems of some 10 % of children with neuromuscular disease and that asthma, reflux, aspiration and bacterial bronchitis can coexist each contributing to symptoms directly. Hence, a multifaceted approach is required for many of those with neuromuscular disease and respiratory problems.

Non-aspiration Respiratory Consequences of GER: Chronic/Recurrent Cough and 'Difficult' Asthma

The relationship between chronic or recurrent cough and GER is controversial with opinions ranging from GER being the major cause of chronic cough to those who believe that it is rarely a significant factor in the absence of significant aspiration [32, 47]. In certain countries, chronic cough is an important indication for surgical intervention despite the lack of any objective published evidence to indicate that this practice is appropriate. The cause for such polarised views is in part due to the difficulties surrounding diagnosis. Identifying GER in a child with a cough is not a rare event since GER is common particularly in early childhood and chronic cough is a common but significantly underrecognised problem, affecting some 10 % of the population in Western countries. The coexistence of the two should not imply causation since they are so common. Moreover, coughing per se can increase the frequency of reflux events [48].

The potential mechanisms through which gastro-oesophageal reflux might induce coughing without aspiration are [19, 20, 25]:

- Inflammation and/or stimulation of the vagus through reflux into the lower oesophagus
- Reflux to the upper oesophagus with stimulation of the cough receptors of the larynx

Persistent and Recurrent Cough

A persistent or chronic cough is one that occurs daily to be distinguished from recurrent coughs. A parent will often report that their child 'always' coughs, but closer questioning reveals that they have frequent episodes with, all be it brief, symptom-free interval periods.

In the adult literature, there are many who believe GER is one of the most common causes of a chronic dry cough [25, 43] though this is debated. The data generated in recent studies in childhood has been far from convincing with a number of studies failing to show a correlation between observed reflux episodes and cough [13, 31]. The proposed mechanism is that a vagal reflex is stimulated leading to coughing. A number of studies using both pH studies and impedance have failed to identify a close correlation between a coughing event either in the period prior to or following the cough [13]. Possible confounding factors might include the fact that 'normal children' cough a number of times during the day and the GER may not be the only cause of cough in a particular child. Moreover, it is clear that coughing can induce GER, and while both are common, ascribing a cause and effect is very difficult.

The reported frequency of GER as a cause for a persistent cough varies widely largely along the lines of 'belief' with reports from the USA suggesting that it may be the commonest cause of a persistent cough in childhood [28], while others in Australia and the UK find it infrequently as an isolated cause for a cough [32, 39]. A systematic review found insufficient evidence from high-quality studies to support the concept of using drugs such as PPI for the treatment of cough other than as a trial in those in whom other interventions have failed [11]. The same authors recently published a study in which there was no correlation between reflux episodes and cough either before or after the cough [13].

'Difficult Asthma'

Generally, there are only three causes of 'difficult' or 'severe' asthma:

- It is not asthma.
- It is asthma and something else.
- The patient is not taking the treatment effectively either because they are not taking their 'preventer' therapy according to the recommended regime [poor regimen compliance often referred to as poor adherence] and/or because they do not use their inhaler effectively [poor device compliance] which may be

due to lack of competence [they have not been taught how to use the device] or contrivance [they know how to use the device but choose not to such as not using a spacer].

Many have sought to implicate GER in 'difficult asthma'. While there is no question that GER can coexist with ongoing respiratory symptoms in those with 'difficult' asthma, it has yet to be shown that effective treatment of the reflux leads to a significant improvement in asthma control. A recent large study in adults found no benefit from pharmacological treatment of GER in a group of asthmatics labelled as having 'difficult asthma' and concluded that speculative treatment was not warranted [33]. Other intervention studies have produced similar negative results [42, 45]. Moreover, many of the therapies used to treat 'GERD' are associated with significant morbidity [5], and hence, speculative therapy should be discouraged.

Summary

Recurrent aspiration of gastric contents either acid or non-acid is undesirable with consequences ranging from occasional cough to chronic pulmonary disease and 'recurrent' chest infections. Those at greatest risk are those with neuromuscular disease and structural problems that compromise the normal protective mechanisms. Investigation of possible aspiration can be challenging and requires a multidisciplinary approach.

The role, if any, of GER without aspiration in causing pulmonary symptoms such as chronic cough and 'difficult' asthma remains to be determined. While respiratory symptoms and GER frequently coexist, it is unclear whether there is any causal relationship and if so in which direction.

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Gastroesophageal Reflux Disease (GERD) and Dental Erosion (DE)

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GERD can result in dental injury by dissolving the inorganic material of the teeth (hydroxyapatite crystals in enamel), which occurs below the critical pH level of 5.5 [1]. This is defined as dental erosion, the irreversible loss of tooth substance without bacterial involvement. This is the most predominant oral manifestation of GERD [2].

Endogenous (intrinsic) acid which originate from refluxed gastric juices (Fig. 106.1) and exogenous (extrinsic) sources of acid which originate from usually dietary, medicinal, occupational and recreational sources are both responsible for the increasing incidence and high prevalence of tooth erosion and associated tooth sensitivity observed in many countries in both children and adults [3]. The severity of dental erosions seems to be correlated with the presence of GERD symptoms and in adults with the severity of proximal eosophageal or oral exposure to an acidic pH [4].

The first modern description of DE associated with GERD is in a case report published more than 35 years ago [5]. In recent years, GERD has been described as an important aggravating factor of DE, and DE is now considered a comorbid syndrome with an established epidemiological association with GERD. As an example, the recently published Montreal Criteria, dealing with a global classification of GERD, state: 'The prevalence of DEs, especially on the lingual and

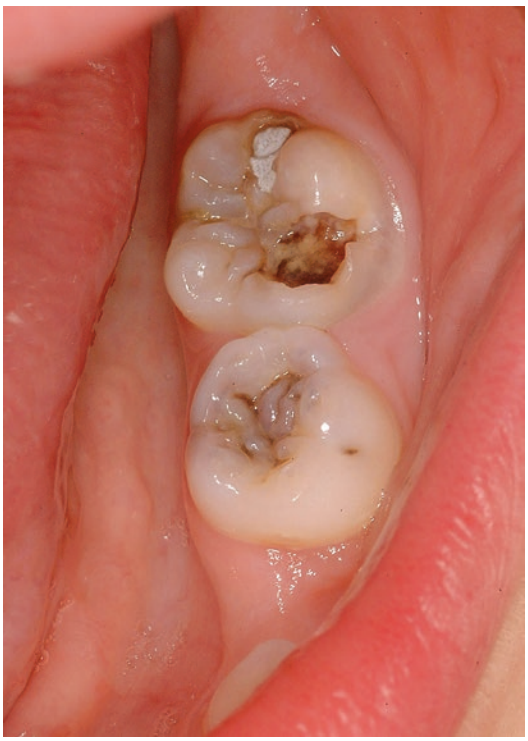

Fig. 106.1 Posterior molar enamel erosion due to acid reflux

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palatal tooth surfaces, is increased in patients with GERD' [6]. This statement (statement no. 48) has been approved with 98 % of agreement among the Montreal Group panellists and, reportedly, is based on a high level of evidence, possibly the highest level of evidence linking GERD with any extra-oesophageal clinical manifestation [6]. Thus, it is not surprising that some authors have advocated that the examination of the oral cavity, in search for 'atypical' DE, should be an integral part of the physical examination of the patient with suspected GERD [7]. On the other hand, other authors have denied, at least in children, that DE may represent a relevant problem in GERD patients [8].

A recent systemic review involving 17 eligible mainly observational and case-control studies of GERD and DE found a strong association between the two conditions [9]. The median prevalence of DE in GERD patients was 24 % and the median prevalence of GERD in adults and in children with DE was 32.5 % and 17 %, respectively. However, there were wide percentage ranges and degrees of tooth tissue loss present among the study populations, and not all studies and evaluations of patients employed oesophageal endoscopy and/or 24-h oesophageal pH metry.

Studies Conducted on Children (See Table 106.1)

A total of five studies were found [8, 10–13]. In the study by Dahshan et al. [10], 37 children undergoing elective upper endoscopy for possible GERD were evaluated for the presence, severity and pattern of erosion and stage of dentition of teeth. It was found that 24 of them had GERD, 20 of whom had DE as well, 10 with mild erosion (tooth score ≤1), 6 with moderate erosion (at least one tooth scored 2) and 4 with severe erosion (at least one tooth scored 3) according to the 4-point score proposed by Aine et al. [12].

In the study by O'Sullivan et al. [8], 53 children with moderate to severe GERD as defined by pH monitoring were examined for DE. No control group was investigated.

Results showed that the prevalence of DE was low when compared with the UK National Survey, with only nine (17 %) of children showing any sign of erosion, and of these, only one had erosion involving dentine.

In the study by Linnett et al. [11], 52 children with a 'definitive' history of GERD underwent a dental examination and were compared on an individual basis with a healthy control sibling without GERD symptoms; the prevalence of teeth erosion was found to be statistically higher in GERD subjects (14 %) than in controls (10 %) ($p < 0.05$). Furthermore, GERD subjects had erosion in more permanent teeth compared with controls (4 % vs. 0.8 %, $p < 0.05$) and more severe erosions.

In the study by Aine et al. [12], 17 children who attended a university hospital paediatric outpatient clinic for GERD and who were found to have pathological reflux at 24-h oesophageal pH monitoring were submitted to dental examination, with teeth erosion scored according to the previously quoted Aine Index (from 0 to 3); no control group was investigated. Overall, two patients had score 0, two patients score 1, six patients score 2 and seven patients score 3, suggesting that only a minority of GERD patients had intact teeth.

Table 106.1 Prevalence of dental erosions in children with GERD

Study (references)	No. patients with GERD	Age (range)	GERD diagnostic method	Prevalence (%)
Dahshan et al. [10]	24/37	2–18 years	Endoscopy	83
O'Sullivan et al. [8]	53	2–16 years	24-h pH metry	17
Linnett et al. [11]	52	17 months–12 years	Symptoms + histology	14
Aine et al. [12]	15	22 months–16 years	Symptoms	87
Ersin et al. [13]	38	6.5 years	Symptoms	NA

NA not applicable

Finally, in the study by Ersin et al. [13], the effects were investigated of GERD on DE vs. caries formation, on salivary function and on salivary microbiological counts. Thirty-eight GERD patients with a mean age of 6.5 years and 42 healthy children of the same age and gender and social background comprised the study group. All subjects answered a detailed frequency questionnaire related to acidic drinks, foods and sugar consumption and underwent a clinical dental examination. The caries experience of the children was recorded according to the World Health Organisation criteria, and erosions were scored according to the Eccles and Jenkins grading scale [14]. The children were also investigated for stimulated salivary flow rate, buffer capacity and salivary mutans streptococci (MS), lactobacilli and yeast colonisation. The results of this rather complicated study are the following: the prevalence of DE and the salivary yeast and MS colonisation was found to be significantly higher in GERD children than in healthy subjects ($p < 0.05$). The caries experience, salivary flow rate, buffering capacities of the children and frequency of acidic drinks, foods and sugar consumption were found to be similar in both groups. The authors concluded that GERD children were at an increased risk of developing erosion and caries compared with the healthy subjects [13].

DE in the intellectually disabled population might be an oral manifestation of GERD, and this group may appear to be at greatest risk [15].

The approach to evaluation and therapy – specifically, the choice of diagnostic tests, duration of therapy, and criteria for cessation of therapy – is unclear. Close consultation with a qualified paediatric dentist is required. The inspection of the oral cavity in search for dental erosions is advisable in patients with known GERD [4].

In conclusion, the fact that dental erosion is a potential risk in children with GERD, whatever the outcome of the studies was, means that paediatricians should be alerted to imply this in their clinical consultation. Children with GERD should routinely be referred to a (paediatric) dentist to quantify the potential erosion risk and, when needed, to intervene and restore the teeth. However, further randomised clinical trials are required to demonstrate that the progression of dental erosion reduces or ceases following gastric acid suppression in patients with confirmed GERD. Collaborative medical and dental management of patients with GERD is strongly advocated [16].

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Part XVIII

Children at High Risk for GERD

The Child with Neuromotor Impairment

107

Christopher D.C. Rittey

Introduction

It has long been recognised that children with neuromotor impairment are at high risk of upper gastrointestinal disorders [1–3]. Symptoms such as rumination, dysphagia and vomiting are a frequent cause of diagnostic difficulty, and upper GI problems contribute greatly to the disability that many children with neurological disease experience.

These problems are a source of considerable anxiety and distress, not only for the neurologically impaired child but also for their family. The management of the child with neuromotor impairment involves careful attention to all symptoms which are medically amenable, and there is no doubt that effective management of gastrointestinal disorders, particularly gastro-oesophageal reflux, can have a substantial benefit both in general well-being and in quality of life.

Cerebral palsy is a common neurological condition with an overall prevalence in Western countries of between 1.7 and 2.5/1,000 live births [4, 5]. This incidence has remained constant for at least the last 20 years despite improvements in neonatal care. Improved medical care has led to significant improvements in survival of the most severely disabled people with cerebral palsy [6]. The groups in which the most significant improvement in survival occurred were immobile children who were fed by others and adults who were fed by gastrostomy. Whereas in the past it was considered that poor growth and weight gain were intrinsic components of cerebral palsy, it is now recognised that effective feeding of children with cerebral palsy is not only possible but an important part of their general care, with improvements in spasticity and mood accompanying improvements in nutrition [7, 8].

This review will consider the conditions which commonly occur in children with neuromotor impairment, their clinical presentation, pathophysiology, management – both medical and surgical – and implications for children and families.

Gastro-oesophageal Reflux (GER)

Chief among the gastrointestinal disorders that present in the child with neuromotor impairment is the issue of gastro-oesophageal reflux. The condition is of considerable importance in the child with neuromotor impairment as it is a cause of considerable morbidity including pain, feeding difficulties, recurrent respiratory infection, abnormal movements and behavioural changes.

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Incidence

A number of studies have reported the overall incidence of gastro-oesophageal reflux (GER) in population of children with neuromotor impairment. Sondheim and Morris investigated 136 severely impaired children who were institutionalised [1]. Of these children, 20 (15 %) had a history of recurrent vomiting, and, of these, 15 (11 %) had gastro-oesophageal reflux proven by radiological examination and/or by demonstration of acid reflux. Complications of GER were noted in a number including oesophagitis (10/14), anaemia (4/14) and aspiration pneumonia (6/14). When compared to the overall population of impaired children, those with gastro-oesophageal reflux had a lower mental age and higher incidence of scoliosis.

Halpern and colleagues reviewed 613 children referred for diagnosis of gastro-oesophageal reflux and noted a significant increase in incidence in children over 1 year of age with neuromotor impairment compared to those without (69 % vs. 47 % $p=0.14$) [9]. Other reviews have described similar rates of GER in children with cerebral palsy [2, 10–13].

Pathophysiology

Improvements in diagnosis of GER have led to increased recognition of its occurrence in children with neuromotor impairment. The use of impedance studies in addition to pH studies allows detection of both acid and non-acid reflux which may be particularly important in the child with neuromotor impairment.

A number of factors have been identified as contributing to the frequency of GER in these children, and these are outlined in Table 107.1. Although many theories as to the cause of GER have been advanced including raised intra-abdominal pressure secondary to increased muscle tone, persistent supine position, seizures or scoliosis [9], it is likely that the predominant factor is intestinal dysmotility which is likely to affect the entire gut.

Clinical Features

The cardinal clinical feature of gastro-oesophageal reflux is vomiting. However, in the child with neuromotor impairment, other symptoms may be more difficult to determine and a high index of suspicion is required. In a systematic review of symptoms associated with gastro-oesophageal reflux, de Veer and colleagues [16] considered symptoms which they categorised as either gastro-oesophageal reflux disease (GERD) symptoms or behavioural symptoms. The symptoms which were shown to be consistently associated with gastro-oesophageal reflux are shown in Table 107.2. Failure to thrive and pain/irritability were symptoms that had contradictory reporting in different studies.

Food refusal, regurgitation, anaemia, recurrent pneumonia and a variety of respiratory symptoms were found not to be clearly related to

Table 107.1 Factors contributing to gastroesophageal reflux in children with neuromotor impairment

Factors contributing to GER in children with neuromotor impairment
Prolonged supine position
Hiatus hernia
Scoliosis
Spasticity leading to increased intra-abdominal pressure
Seizures
Esophageal dysmotility
Decreased lower esophageal tone [14]
Transient relaxations of lower esophageal sphincter [15]

Table 107.2 Symptoms associated with gastro-oesophageal reflux in children with neuromotor impairment

Symptoms associated with GER in children with neuromotor impairment	
"GERD" symptoms	"Behavioural" symptoms
Vomiting	Depression
Rumination	Changed behaviour
Haematemesis	
Wheezing	
Dental erosion	

gastro-oesophageal reflux in this systematic review nor were behaviour problems, self mutilation, aggression or screaming episodes. However, there is some evidence to suggest that these behavioural problems may be more frequent in children with gastro-oesophageal reflux, particularly those with oesophagitis, and this is certainly borne out by clinical experience.

Symptoms of vomiting usually occur during feeds or within a few hours of feeds. If there are additional symptoms such as coughing, choking or gagging, then the clinician needs to consider the additional possibility of oropharyngeal incoordination leading to difficulties with swallowing or even aspiration. In this situation, careful assessment by the speech and language therapist is essential.

Complications of GER

Persistent gastro-oesophageal reflux leads to prolonged exposure of the lower oesophageal mucosa to gastric acid. This results in peptic oesophagitis. The inflamed mucosa may then bleed, sometimes resulting in iron deficiency anaemia. Occasionally, the bleeding may be sufficiently severe as to present with frank haematemesis. Persistent peptic oesophagitis may lead to chronic inflammation and ultimately to the formation of oesophageal stricture. This may present with feeding or swallowing difficulties.

While early treatment of GER can reverse peptic oesophagitis, in children with neuromotor impairment, the diagnosis of oesophagitis may not be considered until late when long-term sequelae are already present. In some children, the only overt sign of reflux is the appearance of behaviour difficulties including agitation and self-injurious behaviour [17]. Neurologically impaired children with oesophagitis are more likely to present with self-injurious behaviour than children without oesophagitis. A high index of suspicion for gastro-oesophageal reflux in children with neuromotor impairment coupled with appropriate early investigation provides the maximum chance of avoiding long-term complications.

Once oesophageal stricture is present, treatment with repeated dilatation and effective anti-reflux therapy is required. Complications of repeated dilatation include perforation, haemorrhage and infection (mediastinitis).

Another complication of chronic gastro-oesophageal reflux is the development of Barrett's oesophagus. This is a condition in which the squamous epithelium of the oesophagus is replaced by columnar epithelium. The most serious consequence of this is the malignant transformation of the columnar epithelium to adenocarcinoma.

A wide range of extra-oesophageal (mainly respiratory) difficulties are associated with GER. Although there is clear evidence that extra-oesophageal symptoms are common in adults with GERD [18], the evidence in children, especially those with neuromotor impairment, is much weaker [19]. Nevertheless, complications including asthma, aspiration pneumonia, bronchiectasis, apparent life-threatening events (ALTE), laryngotracheitis, sinusitis and dental erosion are reported in children with GERD. Impaired oropharyngeal control in children with neuromotor impairment renders these children at increased risk of aspiration, a risk which may be further compounded by uncontrolled gastro-oesophageal reflux. These respiratory disorders may further contribute to nutritional compromise in children with neuromotor impairment leading to a vicious cycle of deterioration. Effective control of GERD is, therefore, an important component of the respiratory care of these children.

Sandifer Syndrome

The association between vomiting with or without hiatus hernia and abnormal dystonic movements of the head, neck and trunk was first noted by Sandifer and reported by Kinsbourne [20]. Since then, numerous reports confirming the association between these movements and gastro-oesophageal reflux have appeared in the literature

[21–23]. The movements typically comprise odd rotational and extensor posturing of the head and neck which commonly occur during or shortly after feeds. The condition is commonly misdiagnosed as other neurological conditions such as epilepsy, movement disorder or behavioural [24–27].

The precise mechanism for the development of dystonia is unknown. Some authors have suggested that the dystonia occurs as a result of reflex spasm of neck muscles due to common sensory innervation of the neck and diaphragmatic muscles. However, the fact that the condition ceases during sleep tends to argue against this proposed mechanism as gastro-oesophageal reflux is known to continue during sleep and the reflex spasm should be likely to continue irrespective of state of arousal. Kinsbourne suggested that there may be a learned element to the phenomenon with the child discovering by chance that the abnormal posture relieved the discomfort associated with GER. There is some support for this contention from the work of Puntis et al. who described improved oesophageal peristalsis on manometry during the abnormal neck movement [28]. Effective treatment of the underlying GERD is usually effective in controlling the abnormal movements, although the resolution of symptoms may be gradual.

Treatment of GER

Medical

Medical treatment for GERD in children with neuromotor impairment follows the same general principles as in children without neuromotor impairment although it is recognised that there is a higher failure rate of medical management in the former and, hence, a greater probability of proceeding to surgical management. The main aim of treatment is to alleviate pain and other symptoms, to aid nutrition, to allow healing of the oesophageal mucosa and to avoid the development of long-term complications.

Initial management centres around modification of feeding. It is important to avoid overfilling of the stomach, and thus, administration of more frequent lower volumes feeds should be advised. If the child is being fed enterally (either by gastrostomy, jejunostomy or nasogastric feeds), it may be necessary to use continuous feeding regimes rather than bolus feeds to achieve this where GER is severe. Although some people recommend placing children in a supine head-up position to reduce gastro-oesophageal reflux, there are few data to support this recommendation.

Thickening of feeds in infants has long been recommended for the management of gastro-oesophageal reflux. The use of thickening agents in children with neuromotor impairment has not been systematically studied. However, Miyazawa et al. studied the use of pectin as a thickening agent in a crossover study of 18 children with cerebral palsy and GERD. This study demonstrated that pectin liquid partially decreased GER as measured by oesophageal pH monitoring [29] and gives some support to the recommendation for thickening of feeds in management of GERD in children with neuromotor impairment. Concerns have been raised that thickeners may be disadvantageous in some children with GERD due to the osmotic effect of thickeners leading to gastric distension [30].

Simple antacids neutralise gastric acid and can reduce symptoms of dyspepsia and oesophagitis. Their major advantage is a rapid onset of action, but they are limited by their inability to maintain the reduction in acidity in the presence of continued acid secretion. Alginate-containing compounds such as Gaviscon or Peptac have the theoretical advantage of forming a “raft” which lies above the surface of stomach contents and which should provide some protection to the oesophageal mucosa. Although there have been questions regarding efficacy in preventing gastro-oesophageal reflux in infants [31], there are data supporting its use in preterm infants [32]. Efficacy has not been specifically studied in children with neuromotor impairment.

Prokinetics

Prokinetic agents play an important role in the management of severe gastro-oesophageal reflux in children with neuromotor impairment. Prior to

its withdrawal from routine use in children, cisapride had been widely used for the management of GERD in children. Although a Cochrane review questioned its general efficacy for the prevention of GERD in children, studies in children with cerebral palsy [33] and in tube-fed children with severe developmental disabilities [34] demonstrated benefit. Attempts were made to maintain supplies of cisapride following the withdrawal of its licence by the Committee on Safety of Medicines due to risk of prolongation of QT interval but the company ceased production in 2005.

The current mainstays of prokinetic therapy include domperidone and erythromycin. Domperidone is now widely used in children with neuromotor impairment. Domperidone is a peripheral D2 receptor antagonist. It acts by increasing gastric motility and reducing gastric emptying time leading to a reduction in postprandial reflux. A review published in 2005 identified only four randomised controlled studies of domperidone in children, none specifically dealing with children with neuromotor impairment. None of these studies provided any data to support the use of domperidone in children with GERD [35]. However, a small prospective study of 20 infants with gastro-oesophageal reflux compared domperidone with cisapride and concluded that both were efficacious [36] although cisapride was slightly more effective at reducing reflux index. One child taking cisapride had a prolonged QT interval.

Erythromycin is a macrolide which has been shown to act directly on motilin receptors in the GI tract resulting in an increase in gut motility. Although there are a number of observational and controlled studies suggesting benefit in preterm infants [37], there are no data regarding its use in children with neuromotor impairment. Nevertheless, it is a safe and well-tolerated drug and deserves consideration in this group of children.

Metoclopramide is a dopamine agonist which enhances the gut response to acetylcholine thus increasing motility and gastric emptying. It also acts to increase lower oesophageal sphincter tone. However, the evidence available does not demonstrate benefit in the treatment of gastro-oesophageal reflux disease [37], and its side effects, particularly sedation, extrapyramidal effects (acute torsion dystonia and tardive dyskinesia) and irritability, have meant that more effective alternative prokinetic agents have taken over.

H2 Antagonists

H2 receptor antagonists act by blocking the H2 receptors of the gastric parietal cells resulting in the suppression of gastric acid production. The current H2 antagonist of choice is ranitidine due to its greater efficacy and lower incidence of side effects. The duration of action of ranitidine requires twice-daily dosing, with thrice-daily dosing required in infants due to a short duration of action. Although widely used in children with neuromotor impairment, the evidence base for its use is limited [38]. There are concerns about tolerance to the antisecretory effect of ranitidine, and gradual withdrawal is recommended when the drug is discontinued due to the risk of rebound hypersecretion.

Proton Pump Inhibitors

Proton pump inhibitors (PPIs) act by irreversibly blocking the H^+/K^+-ATPase pump in the gastric parietal cells, thus inhibiting gastric acid production. They have largely superseded H2 antagonists as the mainstay of treatment for gastro-oesophageal reflux. The most widely used PPIs in children are omeprazole and lansoprazole, and these are generally well tolerated. Studies reveal that short-term treatment with PPIs is effective in healing reflux oesophagitis and improving symptoms of reflux in children although reviews of the data have cast doubt on whether they are useful in infants [39, 40]. Long-term treatment with PPIs has been shown to be effective in maintaining remission of reflux oesophagitis and reflux symptoms in children [41]. Small nonrandomised studies of omeprazole in children with a variety of neuromotor impairments have demonstrated efficacy, and PPIs are probably the medical treatment of choice for GERD in children with neuromotor impairment [42–45].

The main disadvantage of PPIs in children with neuromotor impairment is the lack of an ideal formulation. Omeprazole tablets cannot be broken and omeprazole MUPS have been shown to block small-bore feeding tubes, although they can be dissolved in sodium bicarbonate which reduces the risk of tube obstruction when administered via nasogastric tube or gastrostomy. Lansoprazole may have an advantage for enterally fed children with neuromotor impairment as there are soluble tablets available which can be placed down a feeding tube and studies have revealed that solutions of other formulations in sodium bicarbonate have been shown to be safe for administration via down feeding tubes [46]. Newer PPIs such as pantoprazole have also been shown to be effective [42].

Other Agents

Baclofen is a $GABA_B$ receptor agonist which is widely used for reduction of spasticity in children with cerebral palsy due to its effect on spinal neurones. In addition to this effect, baclofen has been shown to reduce the incidence of transient lower oesophageal sphincter relaxations and possibly to increase sphincter pressure and increase gastric motility [47]. A small observational study of children with neurological impairment revealed that baclofen was effective in reducing vomiting and in reducing the frequency of acid reflux as assessed by pH monitoring [48]. Optimal dosing regimes have still to be established [49]. Newer peripheral acting $GABA_B$ agonists are being developed and tested, but there is no published experience of these in children [50–53].

Surgical

Fundoplication

Although medical treatment of gastro-oesophageal reflux disease in children with neuromotor impairment is always advised as first line, it is well recognised that this group of children have a high incidence of medically refractory reflux. In the past, surgical options were considered the last resort due to the nature of the surgery. The most widely used surgical procedure for controlling gastro-oesophageal reflux was Nissen fundoplication, and this was shown to be highly effective in controlling symptoms [54–56] although surgical complications are reported in up to 59 % of patients [57]. Many of these children have substantial co-morbidities including recurrent respiratory infection, scoliosis, joint contractures, etc., and major thoracoabdominal surgery carried significant risk. Not surprisingly, the rate of complication of fundoplication has been shown to be higher in children with disability [55, 56, 58–61].

However, surgical advances including the development of laparoscopic and endoscopic procedures have markedly reduced the complications of surgery and shortened admission times such that surgical management of GERD in children with neuromotor impairment is a significantly more viable option and these procedures have been shown to be effective [59, 62].

Complications

The most frequent complication of fundoplication in children with neuromotor impairment is recurrence of symptoms due to failure of the wrap or herniation. In this situation, redo of the fundoplication may be worthwhile, but further recurrences are common. In this situation, more radical surgical options such as oesophagogastric disconnection may be a useful alternative, and benefits from these procedures have been obtained in children with neuromotor impairment [63, 64].

Retching is a common and distressing symptom following fundoplication in children with neuromotor impairment [65–68]. It is recognised that children who retch before surgery are very likely to retch after surgery and post-operative retching is recognised as a significant risk factor for failure of fundoplication [66]. It is suggested that retching is due to an inappropriate activation of the emetic reflex due to failure of central control mechanisms in children with neuromotor impairment and that this may be exacerbated by antireflux surgery [68, 69]. Treatment of retching may be decompression via gastrostomy or nasogastric tube or frequent low volume or continuous feeding

or the use of prokinetic agents. Alimemazine may be useful in this situation [70].

Dumping syndrome can occur in up to 30 % of children after fundoplication and occurs in children without as well as with neuromotor impairment [54, 71, 72]. The mechanism is likely to be multifactorial with factors such as increased post-operative gastric emptying and smaller gastric capacity which results in hyperosmolar food boluses in the small bowel causing rapid movement of water from the intravascular space entering the bowel and reducing plasma volume. Hypoglycaemia follows increased secretion of insulin due to the high carbohydrate load in the duodenum. These result in symptoms such as lethargy, pallor, sweating, abdominal discomfort and distension, diarrhoea, etc. Management is by dietary manipulation [73] and by giving small volume feeds or continuous feeding.

Bloating may occur following fundoplication due to an inability to release wind from the stomach. It may result in acute gastric distension and can be relieved by release of gas by nasogastric tube or gastrostomy.

Motility Disorders

As discussed above, gastrointestinal dysmotility is a common problem in children with neuromotor impairment. The enteric nervous system is an extremely complex system, and it should be no surprise that insults to either the central nervous system or the peripheral nervous system should result in dysfunction of enteric neuronal control. While gastro-oesophageal reflux is a major presenting feature of such gastrointestinal dysmotility, specific motility disorder affecting the oesophagus and stomach is well recognised. Additionally, oropharyngeal dysfunction is a major problem, particularly in relation to nutrition.

Oesophageal Dysmotility

Disorders of oesophageal motility are commonly seen in neuromuscular diseases such as dystrophia myotonica, spinal muscular atrophy, myasthenia (both congenital and myasthenia gravis), congenital myopathies and some neuropathies such as hereditary sensory autonomic neuropathies (HSAN) including Riley-Day syndrome [74–79]. Specific visceral neuropathies are also recognised [80]. These conditions usually present with dysphagia or with gastro-oesophageal reflux. Achalasia of the cardia is a cardinal feature of the AAA syndrome (achalasia, alacrima and adrenal insufficiency).

Management of these conditions includes trial of medical treatment to relax the lower oesophageal sphincter, dietary manipulation and, if necessary, surgical procedures such as oesophagocardiomyotomy [77]. Fundoplication for treatment of gastro-oesophageal reflux in these children has been shown to be effective [76, 81–83].

Delayed Gastric Emptying

Delayed gastric emptying is recognised between 28 and 50 % of children with gastro-oesophageal reflux whether or not they have neurological impairment [84]. However, although some early studies suggested that treatment of delayed gastric emptying might be an important factor in effective treatment of GER [85–87], not all authors agreed with this recommendation [88], and more recent studies have not supported this approach [13, 89–92].

Treatment involves the use of prokinetic agents or surgery (pyloromyotomy). Passage of a feeding tube directly into the jejunum or jejunostomy may be necessary.

Nutritional Issues

Oral-motor dysfunction is common in children with neuromotor impairment, and there is a complex interrelationship between incoordination of tongue and oropharyngeal muscles, temporomandibular joint contractures, vomiting and gastro-oesophageal reflux which contributes to poor nutrition. A clear association between the severity of cerebral palsy and the degree of

oral-motor dysfunction and growth failure has been demonstrated [93, 94], and more recent data support this association in children with a variety of neuromotor impairments (predominantly cerebral palsy) [95]. In the latter study, a validated questionnaire was completed and returned by the parents of 266 children. Feeding problems were extremely common in these children with 89 % reported to require help with feeding and 56 % to have problems with choking. Twenty percent of parents described feeding as stressful and unenjoyable. Prolonged feeding times of greater than 3 h/day were reported by 28 %. This study was not able to document nutritional status as 64 % of the children had never had their feeding or nutrition formally assessed.

There is clear evidence that poor nutrition is directly related to feeding dysfunction [96–98] and that children with neuromotor impairment and poor nutrition are more likely to have other health problems including higher surgical morbidity, pressure sore and death [99]. Indeed feeding status is an important predictor of life expectancy in children with cerebral palsy [6]. However, inadequate intake is not the only cause of growth failure in children with neuromotor impairment and central neurological dysfunction, as well as endocrine factors are important. Nevertheless, to a large degree, nutritional status can be improved by improving calorie intake, either by calorie supplementation or, more effectively, by enteral feeding via nasogastric tube or gastrostomy.

Gastrostomy

Gastrostomy has been used for over a century as a procedure to overcome gastrointestinal dysfunction. More recently, it has become popular as the method of choice to feed children with oral-motor dysfunction. Since the introduction of the technique of percutaneous endoscopic gastrostomy in 1980, this has become the procedure of choice for insertion of gastrostomy (see Chap. **).

Despite the enthusiasm for PEG in children with neuromotor impairment, early studies did not provide clear-cut evidence of benefit [99, 100]. Although weight gain was consistently achieved, there was concern that children fed by gastrostomy had a higher death rate, although this was probably due to differences in the degree of disability in the gastrostomy-fed versus orally fed children. However, subsequent studies have suggested that gastrostomy is both efficacious, safe and cost-effective [101, 102].

Complications

Complications from gastrostomy depend to a large extent on the status of the child before placement. Immediate complications include pneumoperitoneum, oesophageal laceration, colonic perforation and peritonitis. Minor later complications are common and include problems such as leakage from the stoma site leading to skin irritation, formation of granulation tissue and local skin infection. More significant problems include tube blockage, tube removal by the child or migration of the tube from the stomach which can be life-threatening. These are rare but important [102].

An important consequence following gastrostomy is the development of gastro-oesophageal reflux. Initial recommendations were that children having gastrostomy should have routine antireflux surgery. However, this view has been questioned, and there is now evidence that although development of gastro-oesophageal reflux following gastrostomy can occur, it is often effectively managed medically, and surgical treatment should be reserved for those children in whom medical management fails [103]. A Cochrane review of this issue concluded that there is still need for better data to direct clinicians as to whether medical or surgical therapy is optimal for children with GER who undergo gastrostomy [104].

Conclusions

Upper gastrointestinal dysfunction is extremely common in the child with neuromotor impairment. These problems may be seen whether the neuromotor impairment is of central or peripheral aetiology, although the majority of data come from children with central disorder, particularly cerebral palsy. Gut

motility problems result in a wide range of upper gastrointestinal manifestations ranging from oral-motor dysfunction to oesophageal motility disorders and gastro-oesophageal reflux. These all conspire to adversely affect the health, nutrition and quality of life of the child with neuromotor impairment and have a substantial effect on parents and carers.

It is important for the clinician dealing with the child with neuromotor impairment to have a high degree of suspicion for such gastrointestinal problems as the presentation may not always be with overt gastrointestinal symptoms. Effective treatment of gastro-oesophageal reflux is an important factor in improving symptoms, avoiding complications and enhancing nutrition in these children. Additionally, careful attention to nutrition in the child with neuromotor impairment is a key element in maintaining health, enhancing quality of life and improving life expectancy. Management of these problems requires a multidisciplinary approach.

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The Obese Child and Reflux

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Abbreviations

BMI	Body mass index
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
HH	Hiatus hernia
LES	Lower oesophageal sphincter
LESP	Lower oesophageal sphincter pressure
MDP	Minimal distending pressure
MTV	Maximum tolerated volume
OR	Odds ratio
TLESR	Transient lower oesophageal sphincter relaxation

Introduction

The obesity and reflux disease epidemics have paralleled each other in modern times. There are global health consequences that will follow this ever-increasing public health problem – an emerging major issue within the school-age and, in some countries, preschool population. We have clearly not yet seen its major effects. There are ethnic and socioeconomic differences in prevalence within regions and between countries, but overweight and obesity are seen in all industrialised and rapidly developing countries, with prevalence at least doubling (and almost tripling) in larger countries like the USA and Canada, Brazil and Chile, Australia and Japan and in Finland, Germany, Greece, Spain and the UK [77]. There are major difficulties in assessing and comparing studies due to the use of different definitions and methodologies, highlighting the need for collaboration and consensus so we can properly assess the relevance and association between reflux, overweight and obesity in children and adults.

Over the last 40 years, we have seen a worldwide increase in serving size, fast food availability and increased use of ready meals, with a likely decrease in eating at set times and much more eating 'on the go' with a likely increase in calorie (and fat) intake for many, given the trend in weights we are seeing in populations, but the absolute effect it has on GERD in children is unclear. There is clear evidence in adults that obesity and GERD are linked through several mechanisms: low baseline resting LESP, increased TLESR, elevated intragastric pressure and anatomical problems such as hiatus hernia, all culminating in worsening reflux. This chapter explores the current evidence for that causal relationship, the known mechanisms as they relate to obesity,

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what long-term upper GI risks are associated with obesity, what specific paediatric evidence there is and what effects weight reduction and medical or surgical treatment might have on reflux management in children. Most current evidence comes from the adult literature and thus highlights the urgent need for effective studies in children.

Obesity and GERD Mechanisms: What's the Evidence?

Why they are linked is not completely known, but there are a number of likely factors which will all potentially contribute to reflux. Whether all are completely relevant to children is uncertain, as there is a lack of literature, but in adults there are six main aspects to consider:

1. *Lower oesophageal sphincter pressure* (*LESP*) *abnormalities*

   One group showed that basal LES pressure was not different to nonobese patients [58]. The relationship between BMI and LESP, however, has been demonstrated in many other studies in adults. In one study in morbidly obese patients, pre and post lap-band surgery subjects had lower basal LESP, with pressure under 10 mmHg identified as a risk factor for GERD and lower than those obese patients with normal acid exposure [30]. In several other studies, those with highest BMI had the lowest LESP, and the number with severe reflux symptoms was higher in the obese and overweight compared to those with normal BMI [15, 43, 67]. A further study in morbidly obese adults showed that those with lower LESP (18%, 59 of 345) were more likely to have symptoms (and abnormal pH and endoscopic oesophagitis) than those with normal pressure. These patients were also more likely to have a hiatus hernia (see section on HH) [72]. LESP was shown to be no different to normals in another study, but the gastroesophageal pressure gradient to LESP ratio was greater during inspiration and may help promote reflux despite no apparent LESP difference [52].

2. *Transient lower oesophageal sphincter relaxation* (*TLESR*) *and its associations*

   TLESR are integral to acid exposure of the oesophagus and independent of swallowing and resting LESP; the main trigger for TLESR is gastric distension, mediated by stretch receptors in the proximal stomach [27, 36, 82, 83]. In a study of three groups of 28 patients, there was a higher rate of TLESR in the overweight and obese groups within 2 h of a meal, and this was associated with greater acid exposure. LES zone shortening occurs in response to gastric distension, and LESP in normal BMI patients is decreased by fatty meals. TLESR correlate with increased BMI and, importantly in adults, waist circumference [82]. Abdominal obesity causes disruption of the GO junction by increased pressure from extrinsic gastric compression (visceral fat and surrounding adipose tissue) and resulting in an abnormal GO pressure gradient [14, 59]. Others demonstrated increased postprandial reflux in overweight and obese patients and showed that BMI and waist circumference were strongly associated with increased stimulation of stretch and tension receptors in the proximal stomach leading to more postprandial TLESR. There was a BMI dose response relationship [13, 59]. Meals eaten in less than 5 min compared to 30 min will increase that rate of TLESR [78]. We know that any type of meal will increase the frequency of TLESR. We know that LES pressure is decreased by fat; some argue that it is the level of fat in our diet (rather than obesity itself) that may drive reflux, but there is insufficient data to fully corroborate this [2].

3. *Hiatus hernia* (*HH*)

   HH is commonly associated with reflux and GERD and is more common in obese adult subjects. One study demonstrated HH in 181 of 345 obese patients (52.6%) [72]. The presence of endoscopic evidence of oesophagitis and HH was more common in obese patients in other studies [69, 79]. Other studies showed that HH is more common in those considered for bariatric surgery and showed that the hernia migrates upwards in those with raised intragastric pressure [71]. Pressure

studies at the GO junction demonstrated raised intragastric pressure, and the abnormal gradient from stomach to oesophagus was correlated strongly with increased BMI. Obese adults are more likely to have an HH, anatomical separation of the LES and crural diaphragm and a raised intragastric pressure during inspiration affecting the gastric pressure gradient, thus promoting upward movement of a hiatus hernia – again waist circumference was associated and independent of BMI, more in men than women [59, 71]. Anatomical changes were also described in obese patients who had computed tomography imaging for Barrett's and demonstrated a 1.5 times increase in adipose tissue in this area compared to controls; although it is an interesting observation, it has not been further explored [59].

4. *Oesophageal body motor abnormalities*

   Most evidence for this is in patients referred for bariatric surgery. Abnormal motility appears common in adults with obesity. Nonspecific motility and nutcracker changes are mostly described in one study (25.6%, 85 of 345) [14]. Manometry is often abnormal, two studies demonstrating obese patients with either nonspecific changes, nutcracker changes or a hypotensive LES. The majority, despite these results, didn't actually have any symptoms, suggesting abnormal visceral sensation in this group [33, 42]. This is much higher than in nonobese and in non-refluxing patients. Most studies in obese patients with GERD demonstrate nonspecific changes and a lower rate of oesophageal clearance of boluses on manometry [28].

5. *Gastric motor abnormalities*

   Gastric motor function and its contribution to GERD are observed using barostatic balloons. Distending pressure required to elicit symptoms was unsurprisingly higher than in lean healthy controls. This is likely another effect of central (truncal) obesity in that the volume required to reach minimal distending pressure (MDP) is elevated. There was also a difference in perception score in refluxers compared to non-refluxers and showed more sensitivity to proximal gastric distension in those subjects [32]. Gastric volume and emptying have been demonstrated as similar to controls, but it is suggested that appropriate satiety signals do not happen and intestinal absorption is greater, possibly through hormonal and autonomic dysfunction [81]. Others have looked at total gastric capacity by assessing maximum tolerated volume (MTV). Unsurprisingly, obese patients had significantly greater MTV than lean controls [21, 23, 31]. In children, an ultrasound study demonstrated a positive correlation of cross-sectional area of the antrum and higher BMI [3]. Gastric emptying (scintigraphy) evidence is actually very old, and studies are contradictory, with some showing accelerated emptying, others revealing no difference [29, 48]. Other studies suggest that obese patients have less high-volume low pH gastric contents after a prolonged fast, suggesting better emptying [25]. This may be important to look at further, as one might expect obese patients to have reduced emptying, suggesting that a large volume, full stomach under external pressure would lend itself to increased TLESR and increased reflux.

6. *Others potential factors*

   Visceral fat is associated with several disorders including diabetes, ischemic heart disease and malignancies. It is a metabolically active tissue and associated with lower levels of protective and pro-inflammatory cytokines, which are overexpressed in Barrett's and erosive oesophagitis, but further work into its effects on inflammation, or reduction in protection, need to be performed [74]. Oestrogen has also been postulated as a factor in women who are obese with GERD – two studies looked at this, but the results do not explain the sex and race differences we see in populations [55, 56].

What Are the Risks of Such Changes in the Obese Population?

Clearly the risk we face in paediatrics is of obese children becoming obese adults and what effect it has on developing truncal obesity and its consequences for diabetes, heart disease and cancers.

What is important about obesity and its association with the upper GI tract is the risk of reflux or other related symptoms, oesophageal erosions and oesophagitis and Barrett's oesophagus and of upper GI cancer, but is it all directly applicable to children? We actually do not really know and must assess the relationship in adult practice.

Most evidence points to a direct dose-dependent association between BMI and reflux [1, 4, 7, 11, 12, 24, 47, 53]. Although the majority of studies show correlation, some have shown no association of increased reflux symptoms and obesity [19, 46]. Positive studies include the ProGERD study in 6,215 patients which demonstrated higher BMI that was associated with more severe heartburn, regurgitation and erosive oesophagitis. This was more pronounced for regurgitation than heartburn, and, only in women, obesity correlated well with erosive oesophagitis [57]. Obesity and the presence of GERD have been looked at extensively using validated questionnaires, but evidence is of moderate strength. Others have looked at erosive oesophagitis, with the NHANES study amongst others demonstrating a positive association [64]. A review by El-Serag showed that there was a 1.5- to 2-fold increase in the risk of reflux disease and erosive oesophagitis and a 1.5- to 2.5-fold increase in cancer compared to those with normal BMI [11].

Studies looking at Barrett's oesophagus and obesity demonstrated mixed results with either no association or an increase in those with high BMI and reflux symptoms or a risk from those with a high BMI alone [22]. Other studies detail a positive association with abdominal girth (truncal obesity), a measurement that is not relevant to children. Abdominal diameter has been reported (not BMI) as a modest risk for Barrett's [5]. Other studies looking at the association of Barrett's and obesity in adults have been variable, with a high BMI and increased risk, to increased risk with the combination of high BMI and GERD symptoms or no risk [12, 22, 66, 68]. Overall, they seem to favour an association, and abdominal obesity was the key factor [9].

Obesity and adenocarcinoma appear to be the strongest association of all (based on recall of symptoms) within patients who have developed oesophageal adenocarcinoma, as opposed to squamous cancer of oesophagus or gastric cancer. This association, seen within studies looking at all three cancers, argues against recall bias but has certainly demonstrated an increased risk in some population-based studies with cancer case controls [6, 44, 45, 76]. Again, properly designed and powered prospective studies would be invaluable to better answer all these questions.

There appears to be no difference between adult males and females for reflux symptoms, but being male and Caucasian (compared to black and Asian males) appears to be a risk for oesophagitis, for Barrett's oesophagus and for oesophageal adenocarcinoma.

Specific Children's Studies: Obesity and Reflux

There are only a few studies in children looking at the association of obesity and GERD.

Størdal and colleagues looked at 872 Norwegian children (median age 10, 65 % male) with asthma (with 264 non-asthmatic controls, median age 10.5, 48 % male) using a validated GERD questionnaire and a derived symptom score, looking primarily at the relationship of reflux with asthma, but also assessing the relevance of BMI, and with a subgroup of 152 who had a pH probe. More asthmatics (21 %) were overweight compared to controls (10.8 %). Overall, asthma and obesity were significant predictors of reflux, but importantly, after further analysis, a dose effect seems likely for BMI; obese children (BMI over 30) and overweight children (BMI 25–30) were more likely to have positive symptom scores compared to controls (35 %, 22.6 % and 16.2 % in the controls). Of those with a positive pH result, there was significantly higher pH detected reflux rate in overweight children; 58 % were overweight, compared to 22 % of controls (OR 4.9) with or without asthma [70].

Elitsur and colleagues in the Eastern USA showed no evidence of increased reflux oesophagitis in overweight or obese children. This was a retrospective chart review of 738 patients (mean

age 10.6 years, with male-to-female ratio of 1.1:1) who had come for endoscopy, 345 (47 %) of whom were either overweight or obese. They used different definitions from the Norwegian study: those with BMI under the 85th percentile normal, 85–95th overweight and over 95th percentile obese. This study did not look at reported symptoms, only histology. There was no difference in histological findings of acid reflux disease in children who were either normal weight, overweight or obese [10].

Another Eastern American study prospectively recruited 236 obese patients (mean age 12.8 years, 45 % males) and with obese defined as BMI over 95th percentile for age and sex (196 patients) and further defined using z-score to define a group of severely obese children (40 patients with BMI z-score >2.7) from the specialist obesity clinic at their centre. They were evaluated using a standard reflux questionnaire and a derived symptom score and compared to an age- and sex-matched group of 191 children with BMI 5th–95th percentile. Similar to other studies, co-morbidities like neurological impairment, respiratory illness and motility disorders were not recruited. They showed that symptoms of heartburn and regurgitation were more common in severely obese compared to obese children and controls and were independent of other risk factors such as smoking or caffeine. An odds ratio (OR) of 7.4 was much higher than the Norwegian study (OR 1.6) and may have been due to the higher proportion of patients who were severely obese, and the study was of a selected obese population [60].

In another retrospective chart review from California, USA, Patel et al. looked at 230 patients (mean age 11.3 years, with 49.6 % male). Of the total, 67 (29.1 %) were above the 85th percentile for BMI (defined as overweight). The study included 51patients (22.2 %) who were scoped because of reflux symptoms. There was no increased prevalence of oesophagitis in the overweight compared to controls (23.9 % vs. 24.5 % controls), but those who were overweight and on medical therapy had evidence of significant histologic changes of reflux oesophagitis compared to overweight children not on medications (34.1 % vs. 7.7 %) [61].

Another group from the USA looked at children enrolled in a health plan between 2007 and 2008; in a population-based cross-sectional study looking at health records of 690,321 patients aged 2–19 years, they evaluated patients using a random sample of 480 children with ICD-9 code for GERD (530.1) from the clinical diagnosis made by clinicians either from history and symptoms or with additional investigations. BMI was assessed using CDC and WHO definitions. They showed that overall GERD was diagnosed in 1.5 % of boys and 1.8 % of girls. There was a slight increase in diagnosis in the non-Hispanic white population. It was not related to obesity in the 2–5-year-old group, but was in the moderately obese and obese 6–11-year-olds and in 12–19-year-olds with moderate (OR 1.16) and extreme obesity (OR 1.32) relating to a 30–40 % increased risk of GERD compared to those of normal weight. The effect was dose dependent and remained after taking helicobacter status, sex and ethnicity into account [41].

Overall, two prospective paediatric studies demonstrated some correlation of obesity with reflux (one with symptom score and pH, the other with the same symptom scoring methodology). Two further retrospective case note reviews looking at histology showed either no difference or only a difference in those overweight patients taking medications for reflux compared to those on none. It is clear that large well-designed and powered controlled studies are required to further define these issues. Koebnick's paper provides additional evidence that obesity is relevant to GERD. No studies appear to have looked at weight-reduction measures, either medical or surgical, in the detail required to draw any conclusions. Further work is clearly needed!

Clinical Implications: Medical Treatment and Operations for Reflux and Obesity

In a large review, the efficacy of lifestyle change in adults was assessed. They looked at evidence levels from 100 selected studies from a total of 2,039 patients between 1975 and 2004. Tobacco

and alcohol reduction and other factors such as specific caffeine, citrus, late evening meals, chocolate and spicy or fatty meals were not significantly associated with improvement in pH or in symptom improvement [37]. The only significant changes were the use of head of bed elevation and weight LESs [36]. A retrospective review of the use of proton pump inhibitors demonstrated similar healing rates of erosive oesophagitis in overweight compared to those of normal weight, suggesting there was no difference in treatment outcome with higher BMI [75].

Surgical Therapy for Reflux in Obese Patients

Surgical therapy and outcomes of reflux post-fundoplication will be dealt with in detail in the relevant chapter, but evidence in several adult studies suggests that obesity is not an indicator of worse outcome [16, 63, 80]. One group showed a high rate of post-op recurrence, correlating with increasing BMI (31 % in those with BMI ≥30, compared to 8 % with BMI 25–30 and 4.5 % in those under 25) [62]. Others have proposed that those with overweight (BMI under 30) might be candidates for fundoplication alone, those with higher BMI (class I, class II or class III) being considered for fundoplication or an anti-reflux bariatric procedure depending on level of BMI and co-morbidities [39].

What About Obesity Management as a Means of Reducing Reflux?

Some have demonstrated the negative effects on reflux when BMI increased by more than 3.5 from baseline (OR 2.8) [32]. Several studies have detailed the independent positive effect of weight LESs on reflux. One study showed those with BMI over 23 who then had a mean weight LESs of 4 kg had a reduction of 75 % from baseline, with a direct correlation of reduction in symptom score and weight LESs [17]. Others reported decreased upright and postprandial pH results in patients with mean weight LESs of 12.4 kg over 13 weeks [49–51]. Despite these positive studies, others show no symptom difference in those randomised to a low-calorie versus unrestricted diet in 20 patients with reflux oesophagitis who all achieved 10 % reductions in weight after 6 months [40]. Others looking at reflux in response to weight LESs in a gastric balloon study showed that a quarter of obese patients had reflux which seemed to improve with sham balloon treatment but was counteracted by actual balloon distension therapy which worsened LES and pH results despite weight LESs [49]. Because it appears favourable in managing reflux, the promotion of weight LESs in obese children would seem logical, given the health benefits it will bring to other systems. Putting this into practice is the challenge, and, again, proper research is necessary to evaluate such programmes.

Surgical Therapy for Obesity

Despite the apparent logic of weight-reduction programmes for obesity and reflux, there is a bigger literature on operative intervention – studies, however, are limited by lack of randomisation, selection differences and how improvements are assessed [1, 8, 18, 65, 73].

There are several procedures developed in adults for obesity:

- Laparoscopic gastric banding
- Roux-en-Y bypass
- Vertical banded gastroplasty
- Gastric balloon distention

Surgical therapy with Roux-en-Y bypass appears to be the most effective procedure in adults, as there is an anti-reflux component to this operation [34, 35, 67]. The ethical issues in children and adolescents have been discussed in two reviews of the current state of play [38, 73]. There is much controversy about the use of such procedures, and although they have been found to be successful in weight-reduction terms, they are clearly not without risks, and the quality of evidence for promoting surgery has been reviewed [54]. A more recent systematic review looked at

eight studies of lap banding in 345 patients (mean BMI 45.8) and Roux-en-Y bypass in six studies with 131 patients (mean BMI 51.8) with average patient age of 16.8 years (range 9–21 years) [73]. They concluded that there were significant and sustained reductions in BMI with both procedures, but evidence of improvement in diabetes and hypertension was at best moderate to weak and enrolment often poor for longer-term follow-up. Presence or changes in severity of GERD were not documented in any of the research. Complications were not insignificant with both lap banding and Roux-en-Y (the procedures where there is most experience), with significantly more severe problems post-surgery in the latter. The importance of pre- and postoperative psychological management was deemed mandatory, and the selection, centre where it is performed and the timing (after the post-pubertal growth spurt) of such procedures are crucial as are the important ethical issues, particularly in children and adolescents [20, 26, 38]. Clearly, more structured and robust research needs to inform the best practice in adults and children and where surgical options sit for obesity in refractory GERD (or its complications) and for other associated health complications. Other endoscopic techniques are emerging such as the Endo-sleeve which is placed in the duodenal bulb and prevents absorption in the duodenum as barrier of plastic material and can be removed when no longer needed endoscopically.

Conclusions and Recommendations

Most evidence we have is from the adult literature. Extrapolation of conclusions from adult data isn't ideal and may not be completely relevant, given that truncal girth seems to be much more relevant than BMI in adults and not in children. Paediatric evidence is scant and somewhat conflicting but would favour the association of obesity and reflux disease. Clearly many obese children become obese adults, so the issue is pertinent to paediatricians and for those transitioning patients to adult care. The suspicion of GERD in obese children should be investigated and treated appropriately and no differently to the nonobese population, but in the knowledge that it is likely to be more common in this group. Weight reduction is surely indicated, given its preventative benefits for other conditions (diabetes, cardiovascular risk and other malignancies) and almost certainly for reflux-related problems. Concerns about progression of GERD to Barrett's and the increased risk of malignancy in adult studies suggest (although seemingly more related to truncal obesity than BMI), make this an important group of children to study. The use of all available interventions needs to be properly assessed and policed! Operative intervention for what is a lifestyle and public health problem has to be carefully assessed. In many respects, the onus on an individual or family to address weight issues has been overtaken by the ability to operate – this is a significant ethical dilemma. Detailed and co-ordinated work should be considered to assess all aspects of associations and efficacy of treatments in overweight and obese children.

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Children at High Risk for GERD: The Premature Infant

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Taher Omari

Introduction

The functioning of the oesophagogastric junction (EGJ) as an anti-reflux barrier is very important to the developing neonate. Gastresophageal reflux (GER) occurs more frequently in the premature infants and term neonates than older children and is typically recognised as 'physiological GER', or benign feed-related regurgitation, which usually resolves spontaneously over time and is not necessarily symptomatic of GER disease (GERD) unless associated with co-morbidities such as failure to thrive, feeding difficulties, irritability in relation to feeding and respiratory complications, including exacerbation of chronic lung diseases and apnoea. GERD in the neonate is different to GERD in the older child and adults in whom chest pain or frequent 'heart burn' is a more common symptom and where long-term exposure of the oesophagus to acid and pepsin results in oesophagitis, dysmotility (e.g. abnormal peristalsis and poor LES tone) and anatomical changes (e.g. strictures, Barrett's oesophagus). Double-blind placebo-controlled trials have shown that, unlike older children, most infants with symptomatic GERD do not respond to acid suppression therapies [1, 2], suggesting that volume, rather than acidity of GER episodes, is the more problematic feature. Furthermore, typical 'GER-related' symptoms are not specific for GERD and may be due to other causes (e.g. allergy); therefore, the differentiation of symptoms due to GER and symptoms due to other causes is a significant challenge for accurate diagnosis.

The physiological mechanisms underlying triggering GER episodes are now well characterised. Most GER episodes are triggered by one mechanism, transient lower oesophageal sphincter relaxation (TLESR). At the present time, however, there are no safe treatments that directly target inhibition of triggering of TLESR.

Upper GI Motility in Infantile GERD

The occurrence of GER episodes and the exposure of the oesophagus to refluxate following the onset of GER are dependent on the motor mechanisms responsible for EGJ competence and oesophageal volume clearance. Factors that influence GER in the premature infant do so by altering these fundamental mechanisms. In infants, most GER episodes extend into the proximal

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oesophagus and often exit the mouth; this is due to the frequent association of abdominal straining with GER and also the higher ratio of gastric volume to oesophageal volume.

Oesophagogastric Junction Competence

The EGJ controls flow of luminal contents between the oesophagus and stomach and comprises the smooth muscle lower oesophageal sphincter (LES) and the crural diaphragm (CD), which functions as an 'external' sphincter supporting the LES (Fig. 109.1a). The EGJ relaxes to allow swallowed food to pass and, in between swallows, is tonically contracted, providing a physical barrier against retrograde flow of gastric contents from the stomach into the oesophagus. The basal EGJ pressure fluctuates over time and during respiration (Fig. 109.1b). The CD is activated during the inspiratory phase of the respiratory cycle and during straining. LES tone varies over time dependent upon fed state and is influenced by many factors: postprandial CCK release, the migratory motor complex (MMC) and methylxanthine therapy to name a few examples. Hence, the measurement of EGJ pressure at a single moment in time may be poorly representative of the 'true' EGJ pressure profile.

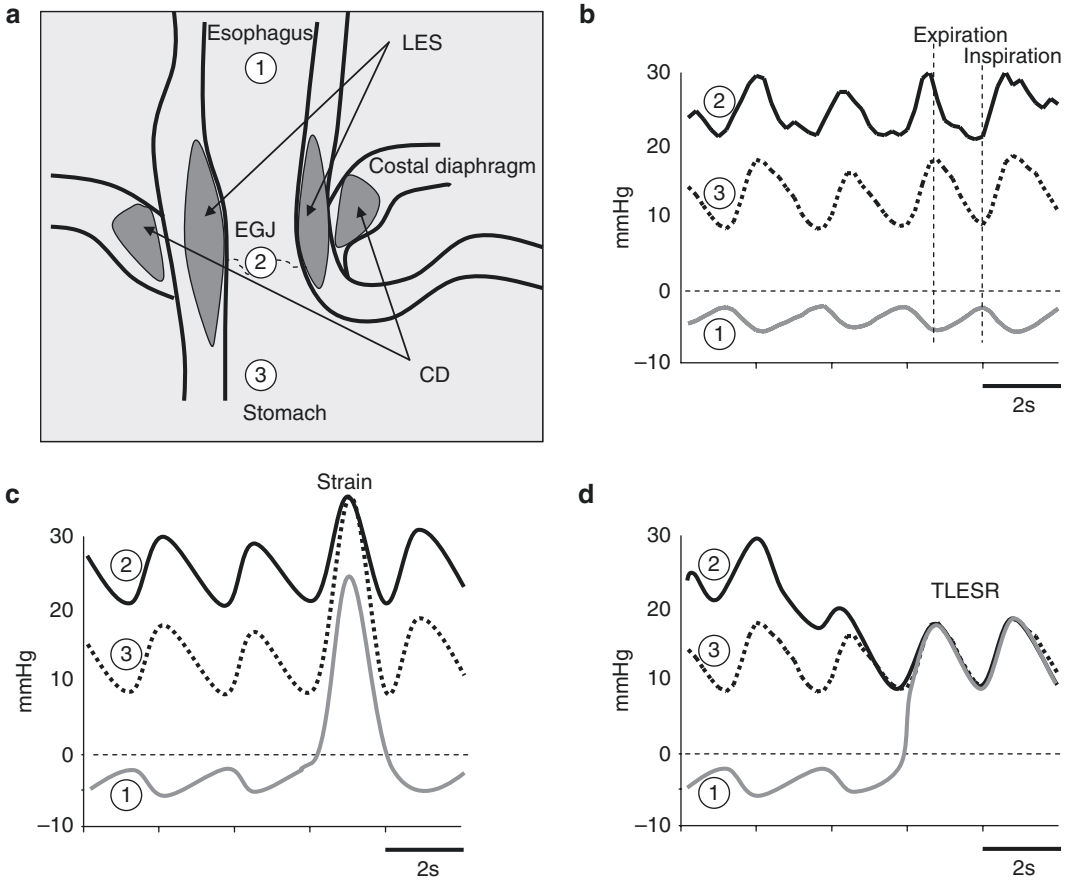

Fig. 109.1 (**a**) Anatomical configuration of the oesohagogastric junction (*EGJ*) and surrounding structures. The EGJ comprises the striated muscle crural diaphragm (*CD*) and smooth muscle lower oesophageal sphincter (*LES*). (**b**) Typical basal pressures across the EGJ. (**c**) Pressure changes typical of abdominal strain-induced reflux. Note that all pressures rise during the strain. (**d**) Pressure changes typical of TLESR-triggered reflux. Note pressures in the LES drop and oesophageal pressures rise, with both equalising to intragastric pressure

As there is a pressure gradient across the EGJ favouring retrograde movement of contents, oesophagogastric 'competence' refers to the ability of the EGJ complex to prevent GER. It is generally thought that an incompetent EGJ is indicated by a low (or poor) basal pressure. The magnitude of the abdominothoracic pressure gradient increases with inspiration and decreases with expiration and is significantly influenced by factors that increase intragastric pressure, such as abdominal staining, or decrease intra-oesophageal pressure, such as increase respiratory effort during airways obstruction. Whilst there is a prevailing view that premature infants have poor EGJ competence, this is in fact incorrect, as prolonged EGJ recordings using the Dentsleeve device have consistently demonstrated resting EGJ pressures in excess of 5 mmHg above intragastric pressure, even in very premature infants.

In the presence of a competent EGJ, GER can therefore only occur in circumstances of elevated intragastric pressure to levels over and above EGJ pressure (e.g. transient abdominal straining) (Fig. 109.1c) or a drop in EJG pressure to levels equal to intragastric pressure (e.g. discrete LES relaxation events) (Fig. 109.1d), the latter being more common.

EGJ Relaxation

Pharyngeal swallowing triggers both LES relaxation and initiates primary peristaltic oesophageal contractions, which can be measured as propagated pressure wave sequences. The onset of EGJ relaxation occurs with pharyngeal swallow, and the EGJ remains relaxed until the oesophageal peristaltic sequence reaches the EGJ, where upon EGJ pressure is reconstituted (Fig. 109.2). In neonates, the period of swallow-related relaxation is comparable to adults, and even very premature infants exhibit a well-developed pattern of swallow-related EJG relaxation [3–5]. Swallow-related EGJ relaxation is

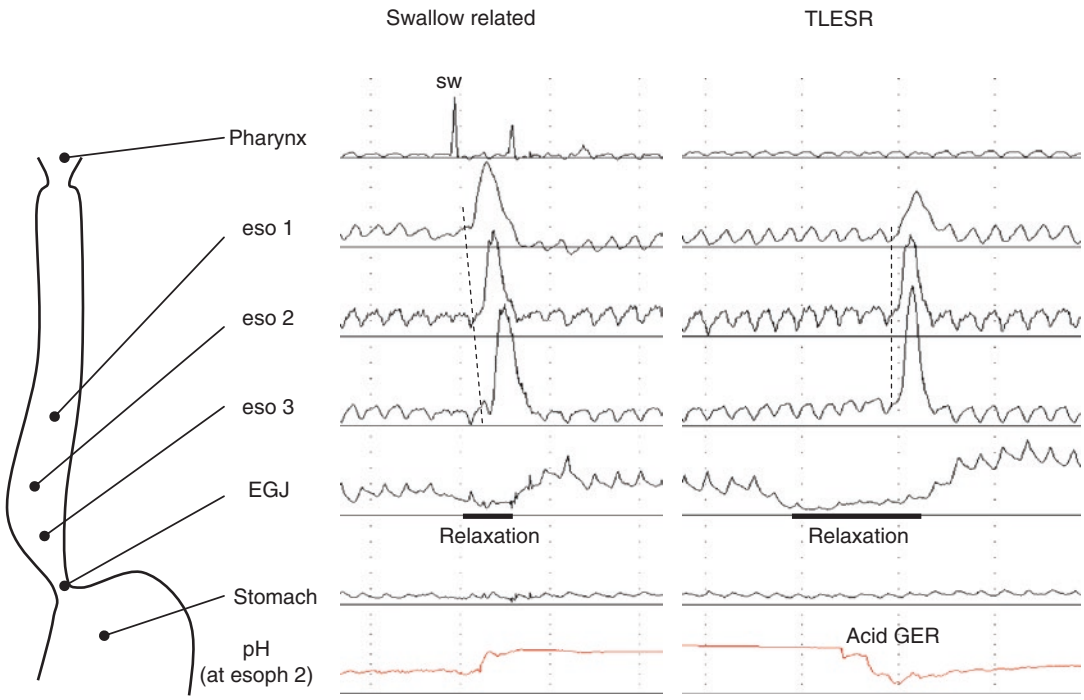

Fig. 109.2 Motility in relation to swallowing and TLESR. Note that the occurrence of pharyngeal swallow (*sw*) initiates primary peristalsis and EGJ relaxation (~3 s duration) triggering acid GER. TLESR is prolonged (~10 s duration), occurs without swallow and in this example triggers acid GER detected by a pH drop

not typically associated with triggering GER, unless associated with failure to initiate peristalsis [4, 6]. Preterm infants often demonstrate a pattern of 'multiple' swallowing, i.e. a sequence of two or more swallows <1 s apart. Such events cause a prolonged more complete relaxation of the EGJ and also inhibition of propagation of oesophageal peristalsis. As such multiple swallowing can be a mechanism of GER triggering.

In addition, the EGJ exhibits transient LES relaxation (TLESR) (Fig. 109.2) which, physiologically, is the mechanism that governs 'belching', venting gas from the stomach to prevent gastrointestinal bloating. TLESR is also the most common mechanism of triggering of reflux. TLESR occurs without pharyngeal swallowing and is prolonged in duration (usually >5 s) and more complete, usually to within 1 mmHg of intragastric pressure. TLESRs have been described in very premature infants and term infants and trigger 50–100 % of GER episodes [4–6].

TLESRs are mediated via a vagovagal pathway initiated by tension receptors located in the proximal stomach [7]. The vagal tension receptors have central terminals in the brain stem (nucleus tractus solitarius) which synapse with neurones of a central programme generator, which is sensitive to a number of other inputs relating to consciousness and body position [8, 9]. Several simultaneous outputs occur following achievement of threshold afferent stimulation of the pattern generator: firstly, the activation of dorsal vagal nucleus motor neurones which project to the LES and lead to smooth muscle relaxation via activation inhibitory motor neurones, and secondly, suppression of excitatory vagal output to the oesophageal body and phrenic nucleus output to the CD, leading to inhibition of peristalsis and inhibition of tonic contraction of the CD [7].

Although this reflex pathway is now well described, the mechanisms that regulate the type of GER (gas, liquid) appear to be more complex than mediated via the single gastric tension receptor reflex. More recent observations suggest that neuroregulatory mechanisms involved can selectively trigger gas over other types of reflux [10], and adult and infant GERD patients with reflux disease appear to selectively trigger more liquid than healthy controls [11, 12]. Also, the rate of gastric emptying, which should affect the degree and duration of gastric distension, does not correlate with triggering of TLESRs [13]. Indeed, recent studies of left/right positioning on gastric emptying and TLESR in infants have shown that right positioning accelerates gastric emptying but paradoxically increases triggering of TLESR [14, 15]. These recent observations, made in preterm infants, suggest that the current accepted model may be too simplistic as it ignores the possibility of secondary mechanisms that contribute to triggering of TLESR in response to luminal contents [16].

Oesophageal Volume Clearance

The motility of the oesophagus, comprising the upper and lower oesophageal sphincters and the oesophageal body, has now been well characterised in premature infants from 26 weeks of gestation to term.

Upper oesophageal sphincter (UES) pressure is generated predominantly by tonic contraction of the cricopharyngeus muscle. With swallowing, the cricopharyngeus muscle is inhibited producing relaxation. The UES is opened by the intrabolus pressure and the superior excursion of the hyoid and larynx [17, 18]. UES function has been investigated in premature infants at gestational ages as young as 33 weeks. In these infants, UES resting tone ranged from 2 to 28 mmHg, and the UES was found to relax appropriately in response to dry swallow [19]. In addition, the magnitude of UES resting pressure is dependent greatly upon the behavioural state with periods of apparent 'comfort' associated with significantly lower UES pressures than periods of activity and apparent 'discomfort' or abdominal straining [19]. Premature infants demonstrate a UES contractile reflex in response to oesophageal distension with air or liquids which demonstrates maturation in terms of stimulus threshold required to initiate the reflex [20–23].

Swallowing initiates primary peristaltic oesophageal contractions, which can be measured as pressure wave sequences propagated in an aboard direction along the length of the oesophageal body. Peristalsis in the premature infants is typically absent in the striated muscle (proximal) oesophagus [24]. However swallow-initiated peristalsis in the smooth muscle (distal) oesophagus has been recorded in the human premature infant down to 26 weeks of gestation [5] and term infants [6]. This peristalsis of the distal oesophagus is essentially *normal* in appearance (propagated following swallow in an abroad direction); however, the rate of propagation of the peristaltic wave is slower in younger premature infants [22]. Premature infants also exhibit spontaneous oesophageal body contractions that occur independently of the usual mechanisms (i.e. swallowing or oesophageal distension). These spontaneous contractions are usually *abnormal* in appearance (i.e. retrograde, synchronous or incomplete propagation) [3, 5, 6] but, being swallow independent, most probably do not appear to impair oesophageal function at least in the healthy infant.

Infusion of fluids and air into the oesophageal lumen triggers reflex secondary peristalsis and reflex swallowing in the premature infants which is volume dependent [20–23]. The mechanisms for clearing refluxate following a GER episode are therefore present and have been shown to effectively clear reflux volume from the oesophagus. Furthermore, the more proximal the reflux episodes, the more likely swallow will be initiated [14] which potentially protects the airway and assists in clearing.

Gastric Emptying

The presence of milk in the fundus stimulates gastric contraction that empties the milk into the duodenum. Gastric emptying is biphasic, i.e. a rapid linear phase which is then followed by a slower exponential phase. Feedback regulation of gastric emptying rate in response the duodenal nutrient infusion is exhibited by infants as young as 32 weeks gestation [25]. As in adults [26], increased caloric density of feeds slows gastric emptying [27, 28]. Studies in premature infants have shown that feed infusion inhibits antral motility and stimulates isolated pyloric pressure waves [29] which serve to regulate fluid flow across through the gastric outlet. The effect of gestational age on gastric emptying rate is not clear.

The relationship between gastric emptying rate and GER is poorly understood. Despite a widely held view that delayed gastric emptying exacerbates GER, there is no evidence of this. Indeed, whilst gastric emptying is most rapid when infants are positioned on the right side (pylorus down), this position is paradoxically associated with *more* GER [14–16], whilst left side positioning markedly delays gastric emptying but decreases GER. The effect of body positioning on GER is directly due to alterations of triggering of TLESR and therefore not simply a function of the location of luminal contents relative to the EGJ outlet (e.g. pooling of contents at the EGJ when positioned right side down). In adults, duodenal infusion of nutrients can trigger TLESR via a mechanism dependent on CCK release [30]. Rapid gastric emptying may therefore exacerbate GER via this mechanism. Alternatively there may be other mechanisms sensitive to the distribution of luminal contents. It has recently been shown that, in right side-positioned infants, TLESRs can be rapidly stimulated with infusion of very small volumes of feed; this interesting observation is difficult to reconcile against known mechanisms of TLESR triggering which rely on gastric distension and/or postprandial release of CCK [16].

Apnoea and Infantile GERD

Apnoea is a major problem in the premature infant, and apnoea is commonly considered to be caused by GERD, particularly if during feeding and/or it is resistant to methylxanthine therapy. Both the distension of the oesophagus during GER and mucosal contact with refluxate have been hypothesised to potentially cause apnoea. The oesophagoglottal closure reflex (initiated by

sensory nerve endings in the body of the oesophagus) is one of a number of reflex responses that can be initiated by oesophageal distension (i.e. GER boluses) that results in adduction of the vocal cords and narrowing of the interarytenoid space and, therefore, whilst providing protection to the airways, may also potentially cause apnoea [31]. An apnoea inducing laryngeal chemoreceptor reflex (LCR) has also been demonstrated in response to laryngeal infusion of water and saline. This is known to exist in human neonates as well as neonatal animal models [32–40] and is proposed as a mechanism of GER-induced apnoea. A direct causal link between GER episodes and apnoea triggering has been explored over many years, and with a variety of methodologies [32–57], the studies are highly inconsistent and, on balance, suggest that, should a causal relationship between apnoea and reflux exist, it is difficult to demonstrate. This is surprising in the light of the fact that the LCR is, in contrast, easily demonstrable in infants with apnoea, and, furthermore, there is clear evidence that as many as 80 % of bolus reflux episodes in infants extend upwards to the proximal oesophagus and pharynx [58].

The effects of stimulation of laryngeal afferent reflexes (such as the LCR) on upper GI tract function have not been studied in detail even though the superior laryngeal nerve (SLN) is the primary afferent neural pathway governing triggering of laryngeal afferent reflexes and the initiation of swallowing, oesophageal body peristalsis and LES relaxation [59]. It has been recently demonstrated that prolonged apnoea episodes (>20 s) in preterm infants are associated with swallowing and LES relaxation, and this appears to bare the hallmarks of LCR stimulation [60] (Fig. 109.3). During such events, the LES pressure preceding apnoea is too high to allow reflux to occur freely (Fig. 109.3). This is potentially clear evidence *against* GER being

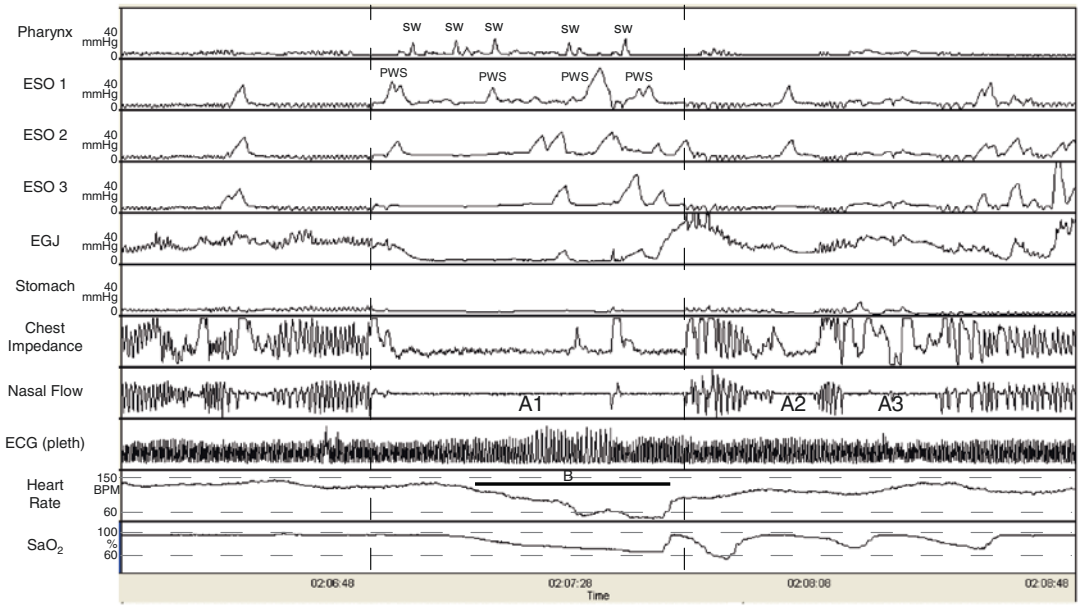

Fig. 109.3 A prolonged mixed apnoea episode (53 s) in a 35-week PMA premature infant. Most probably LCR mediated. The onset and offset of the apnoea episode (*A1*) are marked by *dotted vertical lines*. During the apnoeic period, five pharyngeal swallows (*sw*) occur; initiation of oesophageal PWSs also is apparent. EGJ pressure drops after the onset of apnoea and begins to recover approximately 5 s before the offset of apnoea. Bradycardia (**b**) occurs well after the onset of apnoea. Two additional apnoeic episodes also are apparent (*A2*, 6 s; *A3*, 15 s). Note that these shorter apnoeic episodes, despite causing hypoxia (80 % oxygen saturation), are not associated with swallowing, LES relaxation or bradycardia and thus are unlikely to be LCR mediated (Reproduced with permission Journal of Pediatrics [60])

the predominant trigger stimulus. However, the pattern of LES pressure drop *after* the onset of apnoea may increase the likelihood of reflux occurring in association with straining patterns such as those associated with airways obstruction and cough which are also commonly associated with LCR stimulation. Infants with apnoea unresponsive to methylxanthine therapies are often given anti-reflux therapy. If, however, apnoea is triggering reflux, it is unlikely that anti-reflux therapy will improve apnoea in these patients.

Whilst most studies that directly measure apnoea and reflux have been inconclusive, apnoea and GERD are nevertheless common comorbidities. The pathophysiology of apnoea is clearly complex; however, the main underlying mechanism of apnoea is immaturity or dysfunction of the mechanisms governing control of respiration by the central nervous system. The sites where respiratory and pharyngoesophageal reflexes are processed in the brainstem are very closely related both anatomically and functionally [61]. This neural architecture is essential, for example, for the inhibition of respiration during swallowing (apnoeic pause) to prevent aspiration. Furthermore, the gross neural pathway that regulates the LCR and swallowing involves the same neuroanatomical structures, i.e. involving the superior laryngeal nerve, the nucleus tractus solitarius and vagal efferent neurones (dorsal motor nucleus of the vagus nerve and nucleus ambiguous) [56]. Given the close relationship between neuroregulatory mechanisms governing respiration, apnoea and pharyngoesophageal reflexes, it follows that an immature respiratory pathway (causing apnoea) may correlate with immaturity of the pathways that govern swallowing, reflux triggering and reflux clearing. Hence, the two may be related, due to immaturity of common regulatory mechanisms, however not as 'cause and effect'. It may be possible to test this hypothesis by comparing triggering thresholds for the Santmyer swallowing reflex [62], the oesophageal secondary peristalsis reflex [20–22] and the TLESR reflex [16], in apnoeic infants and age-matched non-apnoeic controls.

Symptom-Based Diagnosis of Infantile GERD

GERD in infants is a complex disorder in terms of the range of clinical presentations, and many patients are diagnosed on 'clinical grounds' alone without further investigations. In most centres, diagnostic testing for GERD is limited to upper GI endoscopy and/or 24-h oesophageal pH monitoring, the former being inappropriate for premature infants, and conclusions based on the latter are heavily weighted on the identification of 'pathological' oesophageal acid exposure (% time oesophageal pH <4). More frequent milk feeding and resultant gastric pH buffering render most bolus reflux episodes 'non-acidic' (pH >4) but does not necessarily reduce TLESRs and reflux bolus overall (Fig. 109.4). Non-acidic reflux is undetectable using standard pH-based reflux detection criteria.

Twenty-four-hour multichannel intraluminal pH-impedance (pH-MII) allows detection of all bolus GER, including gas, mixed liquid-gas or liquid and acidic, weakly acidic or non-acidic GER. The enhanced detection of GER increases the potential for identifying GER as a cause of symptoms such as excessive irritability and crying, feed refusal, cough, apnoea, choking and gagging. Many of these symptoms are not specific to GERD [63] and can be due to other causes, such a food allergies/intolerances, infections or functional gastrointestinal disorders such as infantile colic or constipation [64]. With evidence now emerging that empirical prescription of acid suppression therapy to infants is largely ineffective and potentially harmful [1], more precise diagnostic testing offers the potential for anti-reflux therapy to be better targeted at patients in whom symptoms can be demonstrated to be due to acid GER and/or bolus GER.

Current guidelines from North American Society for Pediatric Gastroenterology, Hepatology and Nutrition and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition [65] advocate the use of pH-MII for the investigation of symptoms such as unexplained crying and/or distressed behaviour, apnoea and apparent life-threatening

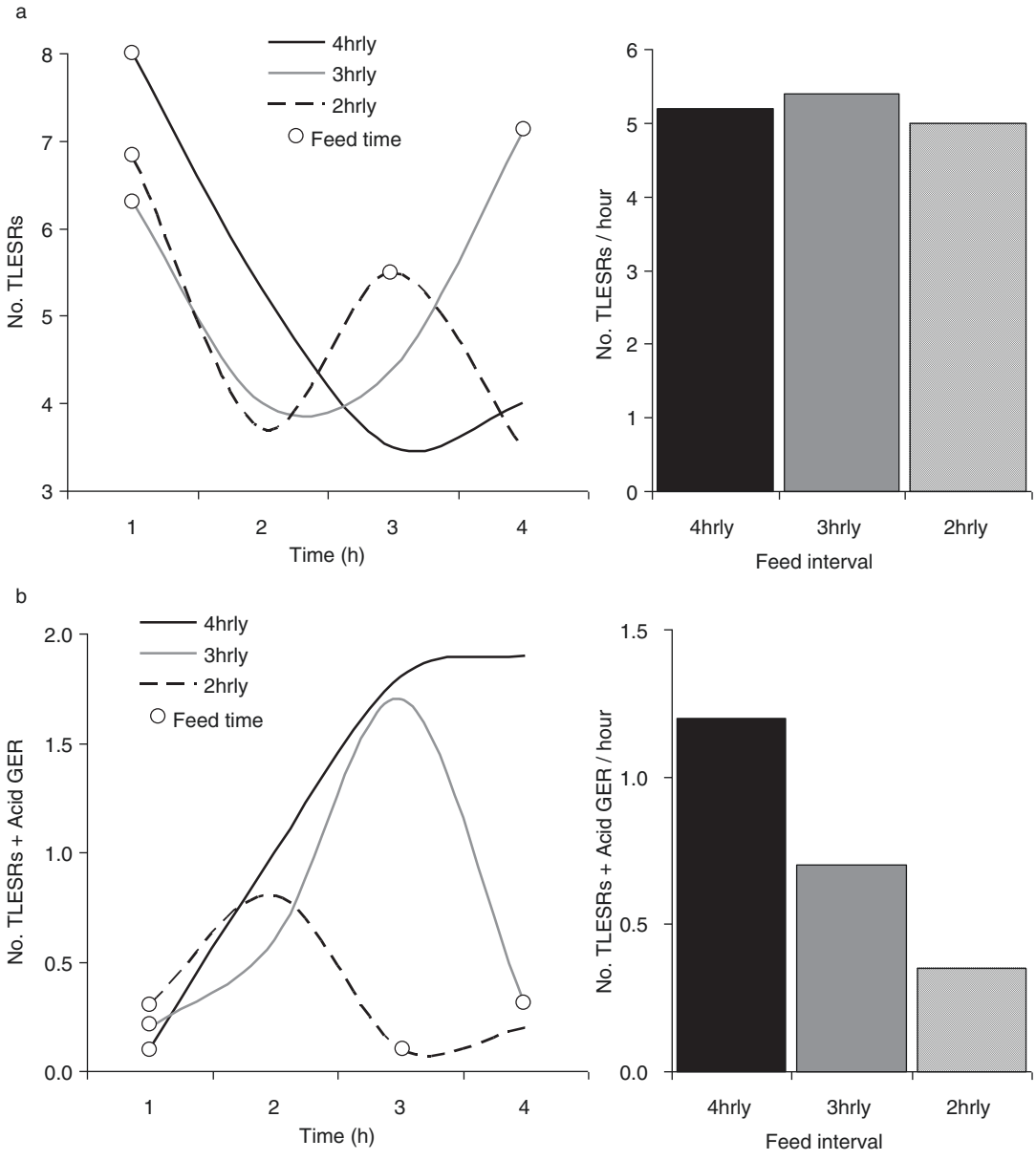

Fig. 109.4 Effect of feeding frequency on the number of TLESRs recorded over a 4 h period. (**a**) As feeding stimulates TLESRs via gastric distension, there is no net effect of more frequent (lower-volume) feeding on the number of TLESRs overall. (**b**) As feeding buffers gastric pH, there is a reduction in the number of TLESRs that trigger GER with refluxate pH in the 'acidic' range (pH <4)

events. Studies in infants, children and adults [5, 6] have characterised the impact of GER episode detection by pH-MII monitoring on diagnosis of GER-symptom associations. When compared with pH-metry alone, pH-MII has been consistently shown to increase the yield of patients in whom a positive GER-symptom association can be demonstrated [66]. The degree of GER-symptom association is best defined using symptom association probability (SAP) which is derived from the statistical probability (P) that GER episodes and symptoms are temporally

related using a Fisher exact test (SAP = [1 – P]*100) [67]. The reported strength of the SAP is that it takes into account the number of time intervals with associations, the number of non-associated intervals (reflux or symptom) and the number of 'empty' intervals (neither reflux nor symptoms). The SAP is therefore less likely to be influenced by the overall number of symptoms/reflux episodes.

Despite what appears to be an improvement in diagnostic methodology, all prolonged 24h reflux monitoring studies need to be interpreted in the context of the vagaries of such tests as currently applied. Firstly, the test assumes that symptoms occurring following reflux are *caused* by reflux; this relationship is yet to be proven by way of outcome studies showing that a high SAP can predict of symptomatic improvement with anti-reflux therapy. Furthermore the tests are far from perfect, and the reliability of the findings are heavily influenced by the diligence of individuals charged with the task of marking symptom episodes when they occur and those responsible for pH-impedance analysis which (in the author's experience) suffers from poor interrater reproducibility across different centres. The standard GER-symptom association interval used is 2 min and was originally based on investigations of heartburn symptoms in adults [67]. However, the optimal time window may be influenced by both the time from reflux to the onset a symptom and the time required to press an event button having noticed the symptom. Some symptoms may be missed entirely or marking significantly delayed due to preoccupying factors. Whilst synchronous video monitoring would enable a more accurate assessment of behaviours associated with onset of GER episodes in infants [68], this approach is unavailable in most centres and is very time consuming in analysis.

Therapy for Infantile GERD

When faced with a premature infant with a reflux-related problem, non-pharmacological therapy can help, and in many cases, symptoms will improve with time and development without intervention. Elevation of the head of the bed, antacids and feed thickeners are usually recommended. Of these measures, feed thickeners have been shown to significantly reduce the incidence of regurgitation and impedance-detected bolus reflux [69, 70]. More frequent lower-volume feeding is a measure that reduces the acidity of bolus reflux; however, it does not reduce bolus reflux overall (Fig. 109.4). The evidence for antacids and cot elevation is largely anecdotal; however in older infants, a range of non-pharmacological therapies in combination (including use of hypoallergenic formulas) does appear to reduce reflux symptoms [71].

In contrast to non-pharmacological approaches, medical therapies for GERD are largely untested in the premature infants. Currently proton pump inhibitor (PPI) therapy is widely used; however, there is little evidence showing that acid suppression reduces reflux-related symptoms, unless use is guided by evidence of extreme levels of oesophageal acid exposure [72]. Other approaches to GERD include pro-motility agents such as cisapride, metoclopramide or erythromycin which improve oesophageal volume clearance, LES pressure and/or gastric emptying, but their effects on reflux are largely unproven and side effects are common and problematic [73–76]. The GABA(B) agonist baclofen has been shown in older children to reduce reflux by inhibiting TLESRs [77]; however, common side effects such as respiratory depression preclude use in premature infants. The compound (R)-(3-amino-2-fluoropropyl) phosphinic acid (Lesogaberan) has recently been described [78]. Lesogaberan is a peripherally acting GABA(B) agonist with an equivalent action to baclofen but potentially with fewer side effects [79, 80]. This therapeutic approach may have significant clinical utility in that it reduces bolus reflux, something that PPI therapy is incapable of doing [72]. The potential to use a combination of PPI and reflux inhibitor therapies, particularly in infants with high oesophageal acid exposure and a positive symptom-reflux association, is tantalising; however, there are no safety data presently available to predict if reflux inhibitor therapies targeting TLESRs will be safe to use in infants.

As previously described, left side body positioning reduces reflux by reducing triggering of TLESRs and moving gastric contents away from the EGJ [81]. Although left-side positioning also slows gastric emptying, there is no evidence of gastric emptying time contributing to infantile GERD [14]; indeed slower emptying may potentially be an *advantage* as it may prolong acid buffering, improve infant satiety and reduce the postprandial release of CCK which may further reduce reflux through reduced TLESR triggering. As this is the case, left-side body positioning may have some therapeutic potential. Whilst the risk of accidental rolling to the prone position when on the left side precludes use of this approach in older infants in the community (due to contraventions of SIDS safe guidelines), this is less of a concern in hospitalised premature infants who are closely monitored as a routine.

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Part XIX

The Stomach

Embryology of the Stomach

110

Mike Thomson

Function of the Stomach

The stomach, as a J-shaped dilation of the alimentary canal, is continuous with the oesophagus proximally and the duodenum distally. Its functions primarily include the bulk storage of undigested food, mechanical breakdown of food, disruption of chemical bonds via acids and enzymes (pepsin) and production of intrinsic factor, allied with very little absorption of nutrients.

The stomach releases its contents in a controlled fashion to accommodate the much smaller capacity of the duodenum. The stomach volume ranges from about 30 ml in a neonate to 1.5–2 l in adulthood [1].

Embryology of the Digestive Tract

During the embryological period, the digestive tract is divided into segments based on vascular supply:

- Foregut (oesophagus, stomach, part of duodenum, biliary apparatus) is supplied by the celiac artery.
- Midgut (rest of small and large bowel up almost to the splenic flexure) is supplied by the superior mesenteric artery, and the hindgut (rest of large bowel to superior part of anal canal) gained its blood supply from the inferior mesenteric artery. The foregut derivatives are the pharynx and its derivatives, the lower respiratory tract, the oesophagus, the stomach, the duodenum as far as the entrance of the common bile duct, the liver, the pancreas and the biliary apparatus. All except for the pharynx, respiratory tract and upper oesophagus are supplied by the celiac artery

The foregut extends from the buccopharyngeal membrane to the duodenum. It is initially located in the median sagittal plane and is attached by mesentery to the anterior and posterior abdominal walls [2, 3].

During the solid stage of development, the endoderm of the gut tube proliferates until the gut is a solid tube. A process of recanalization restores the lumen.

Embryology of the Stomach

In the middle of the fourth week, a fusiform dilatation appears in the caudal part of the foregut that indicates the site of future stomach. It links the pharynx to the primitive midgut. The dilatation oriented in the midline enlarges and broadens ventrodorsally (Figs. 110.1 and 110.2). By the fifth and sixth week, the dorsal border grows

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much faster and forms the greater curvature, whereas the ventral border forms the lesser curvature. Two positional shifts bring the stomach to its adult configuration. By the seventh to eighth week and as stomach enlarges, it slowly rotates 90°, clockwise around its longitudinal axis. As a result, the ventral border moves to the right and the dorsal border to the left with the right side becoming the dorsal surface and the left side becoming the ventral surface. Initially the two ends of the stomach lie in the midline. During rotation, the cranial end moves to the left and slightly ventrally, and the caudal end moves to the right and dorsally [4].

The early stomach is suspended from the dorsal body wall by a portion of the dorsal mesentery called the dorsal mesogastrium. It is connected to the ventral body wall by a ventral mesentery that also encloses the developing liver [4].

Since the stomach is attached to the dorsal body wall by the dorsal mesogastrium and to the ventral body wall by the ventral mesogastrium (Fig. 110.3), its rotation and disproportionate growth alter the position of these mesenteries. Rotation about the longitudinal axis pulls the dorsal mesogastrium to the left, creating a space behind the stomach called the omental bursa (lesser peritoneal sac) (Figs. 110.3, 110.4, and 110.5). This rotation also pulls the ventral mesogastrium to the right. As this process continues in the fifth week of development, the spleen primordium appears as a mesodermal proliferation between the two leaves of the dorsal mesogastrium (Figs. 110.3 and 110.4). With continued rotation of the stomach, the dorsal mesogastrium lengthens, and the portion between the spleen and dorsal midline swings to the left and fuses with the peritoneum of the posterior

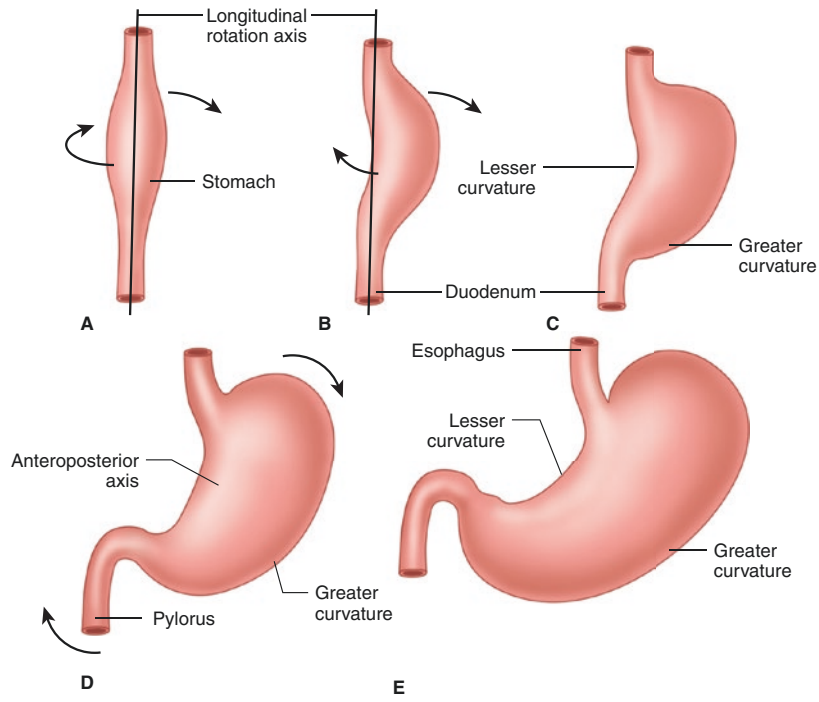

Fig. 110.1 Rotation of the stomach. (**a**–**c**) Rotation of the stomach along its longitudinal axis as seen anteriorly. (**d**, **e**) Rotation of the stomach around the anterior axis. Note the change in position of the pylorus and cardia

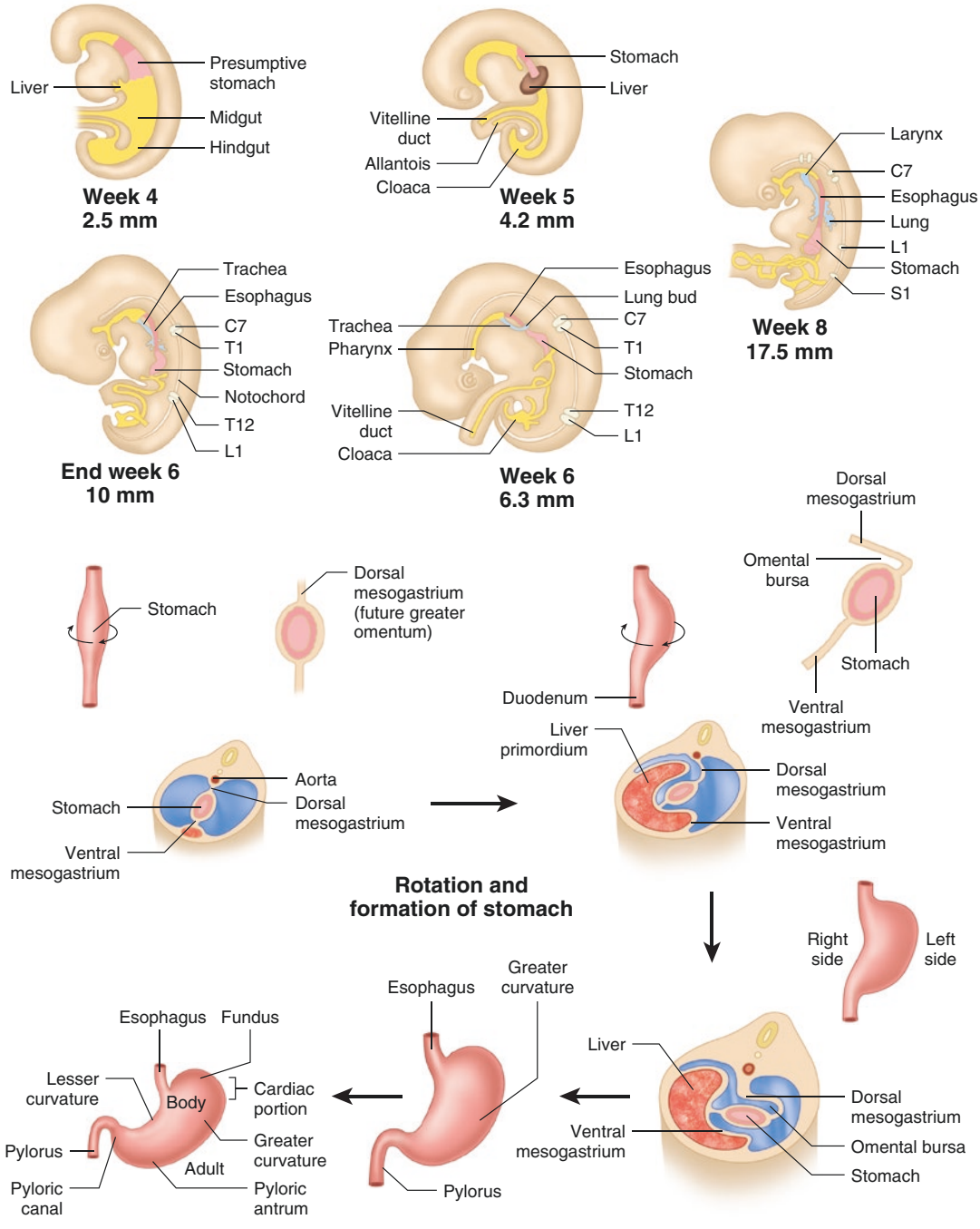

Fig. 110.2 Embryology of stomach

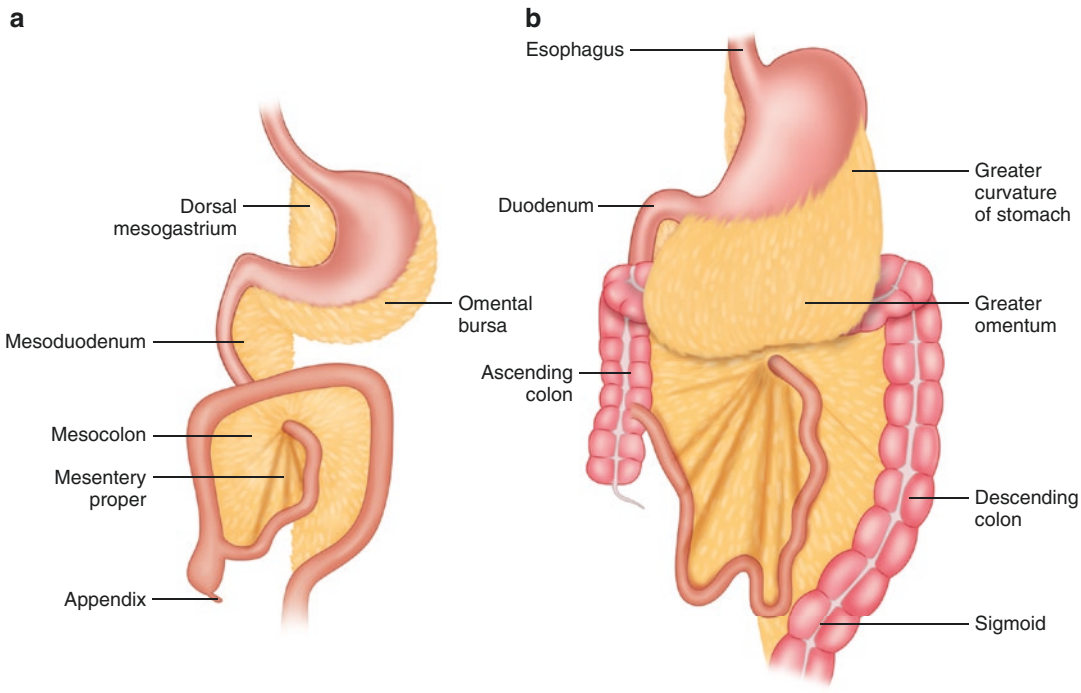

Fig. 110.3 Dorsal mesentery derivatives. (**a**) Derivatives of the dorsal mesentery at the end of the third month. The dorsal mesogastrium bulges out on the left side of the stomach, where it forms part of the border of the omental bursa. (**b**) The greater omentum hangs down from the greater curvature of the stomach in front of the transverse colon

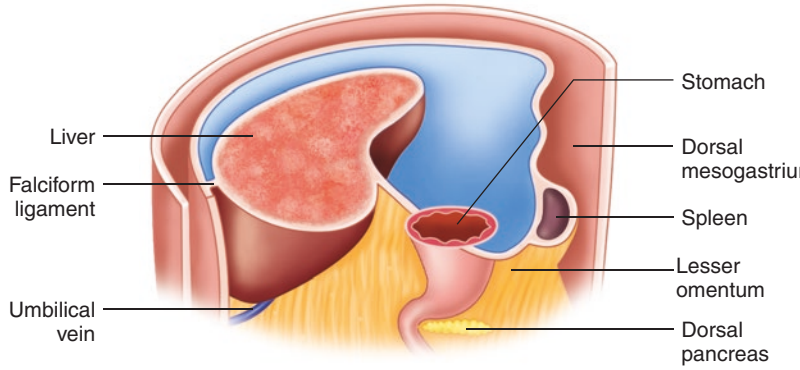

Fig. 110.4 Coronal view through the stomach and mesenteries. Transverse sections through the region of the stomach, liver and spleen, showing formation of the omental bursa (lesser peritoneal sac), rotation of the stomach and position of the spleen and tail of the pancreas between the two leaves of the dorsal mesogastrium. With further development, the pancreas assumes a retroperitoneal position

abdominal wall (Figs. 110.3 and 110.4). The posterior leaf of the dorsal mesogastrium and the peritoneum along this line of fusion degenerate. The spleen, which remains intraperitoneal, is then connected to the body wall in the region of the left kidney by the lienorenal ligament and to the stomach by the gastrolienal ligament [5].

The events also explain the vagal innervations of the stomach: the right vagus nerve innervating

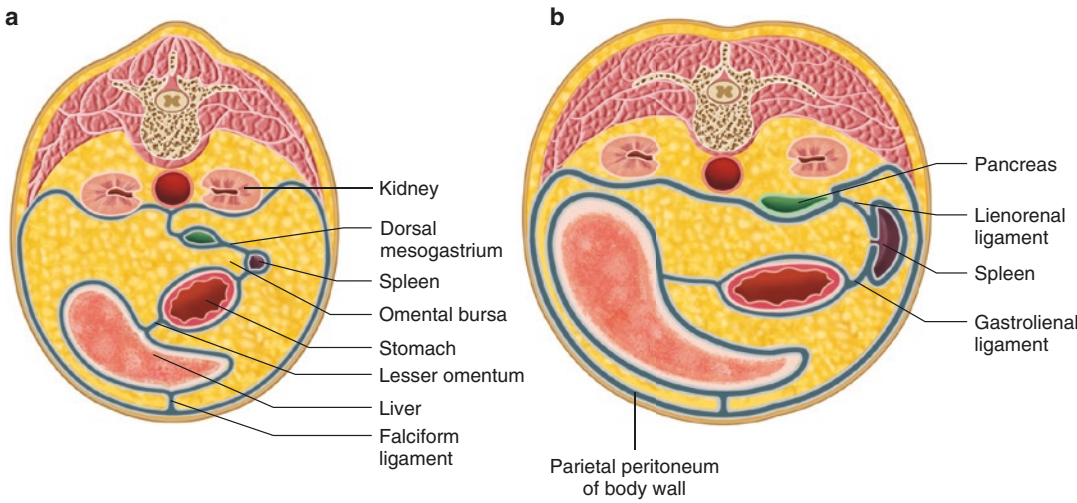

Fig. 110.5 Transverse section through the stomach showing the formation of omental bursa

the posterior stomach wall (the primordial right side) and the left vagus nerve innervating the anterior wall [6].

Position of the Stomach

With the development of the oesophagus, the proximal end of the stomach migrates caudally through the following vertebral levels: C2 (at week 4), T2 (at week 6) and T10 (at week 8). The caudal shifting of the entire foregut comes to an end with the formation of the diaphragm and the resulting fixation of the oesophagus-cardia passage as well as the formation of the vessel-pancreas-stalk at the level of the duodenum. At 12 weeks, the cardia is fixed at the level of T11, and the pylorus is fixed at the level of L1 as a result of the duodenal development and fusion of the posterior peritoneum [7].

The gastroesophageal orifice is the most fixed part of the stomach. The fundus fits into the curve of the left dome of the diaphragm. The pyloric part is very mobile. The greater curvature may even enter the true pelvis and forms the left lower stomach border, whereas the lesser curvature forms the right upper border. Posteriorly, portions of the pancreas, transverse colon, diaphragm, spleen and apex of the left kidney and adrenal gland bound the stomach. The posterior wall of the stomach actually comprises the anterior wall of the omental bursa or lesser peritoneal sac. Anteriorly the liver bounds the stomach, whereas the inner aspect of the anterior abdominal wall bounds the anterior left lower aspect. The stomach lies on a variable visceral bed that includes the diaphragm, pancreas and transverse mesocolon. Posterior gastric ulcers may involve the pancreas and the splenic artery, resulting in severe pain and bleeding.

The stomach is completely invested by peritoneum, except for a small bare area at the gastroesophageal junction. This peritoneum passes as a double layer from the lesser curvature to the liver as the gastrohepatic portion of the lesser omentum and then hangs down from the fundus and greater curvature as the greater omentum, extending to the transverse colon (as the gastrocolic ligament), spleen (as the gastrosplenic ligament) and diaphragm (as the gastrophrenic ligament).

Stomach Parts

The stomach is divided into four regions that can be defined by anatomic or histologic landmarks. Anatomically the cardia is a small ill-defined area of the stomach immediately adjacent to its junction with the oesophagus. The fundus projects upwards, above the cardia and

gastroesophageal junction. This dome-shaped area of the stomach is its most superior portion and is in contact above with the left hemidiaphragm and to the left with the spleen. The body, or corpus, the largest portion of the stomach, is located immediately below and continuous with the fundus. The incisura angularis, a fixed, sharp indentation two thirds of the distance down the lesser curvature, marks the caudal aspect of the gastric body. The gastric antrum extends from its indistinct border with the body to the junction of the pylorus with the duodenum. These gross anatomic landmarks correspond roughly with the mucosal histology because antral mucosa (pyloric gland mucosa) actually extends from an area on the lesser curvature somewhat above the incisura. The caudal end of the stomach is physiologically separated from the small intestine by the muscular pyloric sphincter [8].

The Tissue Layers

The luminal surface of the gastric wall forms thick, longitudinally oriented folds, or rugae, that flatten with distention. Four layers make up the gastric wall: mucosa, submucosa, muscularis propria and serosa (Fig. 110.6).

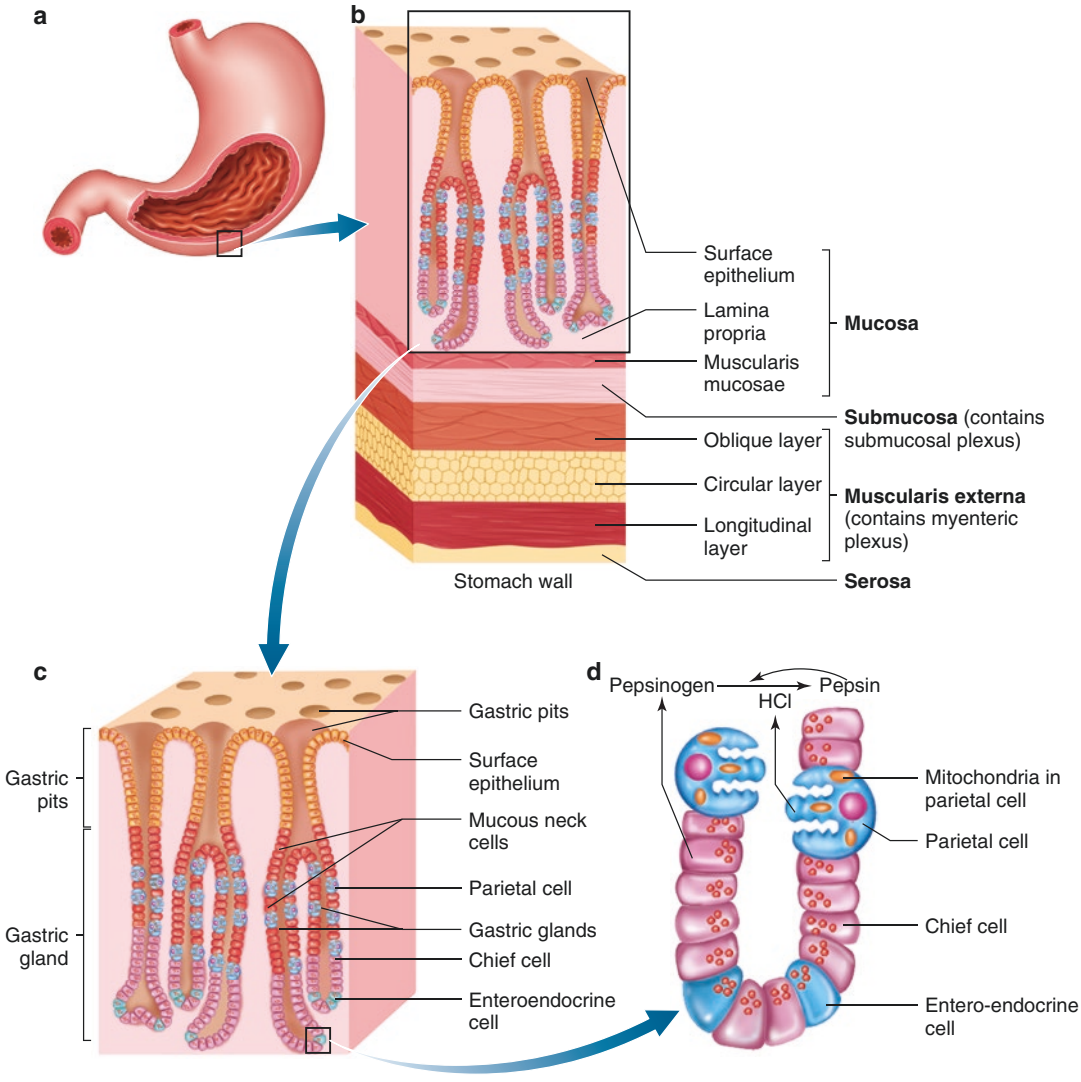

Fig. 110.6 Histology of the gastric gland

Mucosa lines the gastric lumen, appearing as a smooth, velvety blood-filled lining. The mucosa of the cardia, antrum and pylorus is somewhat paler than that of the fundus and body. It is within the gastric mucosa that most of the functional secretory elements of the stomach are located.

The submucosa, immediately deep to the mucosa, provides the dense connective tissue skeleton of collagen and elastin fibres. Lymphocytes, plasma cells, arterioles, venules, lymphatics and the submucosal plexus are also contained within the submucosa.

The third tissue layer, the muscularis propria, is a combination of three muscle layers: inner oblique, middle circular and outer longitudinal. The inner oblique muscle fibres course over the gastric fundus, covering the anterior and posterior aspects of the stomach wall. The middle circular fibres encircle the body of the stomach, thickening distally to become the pyloric sphincter. The outer longitudinal muscle fibres course primarily along the greater and lesser curvatures of the stomach. The final layer of the stomach is the transparent serosa, a continuation of the visceral peritoneum. Connective tissues and smooth muscle are derived from splanchnic mesoderm.

Histological Differentiation of the Stomach

The gastric epithelium including hormone-secreting specialised gastrointestinal cells, gastric pits and gastric glands are derived from the foregut endoderm. The muscular walls of the stomach (lamina propria, muscularis mucosae, submucosa, muscularis externa, adventitia and/or serosa) are derived from splanchnic mesoderm.

At the histological level, development of fetal gastric mucosa occurs very early during fetal life. Between 11 and 17 weeks, the stratified surface of epithelium is replaced by a simple layer of columnar epithelial cells. The surface mucus cells, which are similar throughout the stomach, produce mucus. Mucus, along with bicarbonate, is luminal cytoprotection from acid, pepsin, ingested substances and pathogens.

The first pit/gland structures are observed at 11–12 weeks of gestation. When the surface epithelial lining invaginated by gastric pits, or foveolae, that provide the gastric glands access to the gastric lumen. The gastric mucosa is organised in vertical tubular unit consisting of an apical pit region, and isthmus, and the actual gland region that forms the lower part of the vertical unit (Fig. 110.6). The progenitor cell of the gastric, which is localised in the isthmus, gives rise to all epithelial cells. The mucus-producing pit cells migrate up towards the gastric lumen, and acid-secreting parietal cells (oxyntic migrate downwards to the middle and lower regions of the gland. Chief (zymogenic) cells secrete pepsinogen and predominate at the base of the glands. Neuroendocrine cells, including enterochromaffin cells (serotonin), enterochromaffin-like cells (histamine) and D cells (somatostatin), are also present at the base of the gland [8].

The gastric glands of different anatomic regions of the stomach are lined with different types of specialised epithelial cells, allowing for differentiation of these regions by type of gastric gland.

The stomach's most proximal region, the cardia, is a small transition zone from oesophageal squamous epithelium to gastric columnar epithelium. The cardiac glands are mostly populated by mucus-secreting or endocrine cells. The cardiac pits are irregular and shallow; the ratio of the lengths of pit to gland is approximately 1:1.

There is a gradual transition from cardiac glands to the second region, the acid-secreting segment of the stomach. This region encompasses the gastric fundus and body and contains the oxyntic glands. These glands are long and deep with straight pits. The ratio of the length of pit to glands is approximately 1:4. It has parietal (oxyntic) cells that secrete hydrochloric acid and intrinsic factor, chief (zymogen, peptic) cells that secrete pepsinogen, endocrine cells and mucus neck cells. Of note glands become functional and secrete HCl and enzymes at 8–9 months of gestations.

The final region, corresponding to the antrum and pylorus, contains the pyloric glands, composed of endocrine cells, including gastrin-producing G cells and mucus cells. The glands here are characterised by deep pits but short glands, with a pit to gland ration close to 1:1.

Mucus is also secreted along with bicarbonate, by the surface mucus cells between glands. Surface mucus cells secrete neutral mucus, rather than sulphated mucus separated by mucus neck cells, which reside in close proximity to parietal cells. The surface mucus cells are cytoprotective, whereas the mucus neck cell functions as a stem cell precursor for surface mucus parietal, chief and endocrine cells [9].

Blood Supply

Gastric blood vessels are derived from the splanchnic mesoderm. The arterial blood supply of the stomach is from the celiac trunk: (1) the right gastric (from the hepatic) and left gastric arteries run along the lesser curvature; (2) and the right gastroepiploic (derived from the hepatic) and left gastroepiploic and short gastric (from the splenic) arteries course along the greater curvature. The venous drainage of the stomach generally accompanies the arterial supply. The veins empty directly or indirectly into the portal vein. The connections between the left gastric and oesophageal veins are important portal-systemic anastomoses (Fig. 110.7).

Lymphatic Drainage

Most of the lymphatic drainage of the stomach eventually reaches the celiac nodes after passing through intermediary lymph nodes. Lymphatic plexuses drain into regional nodes that accompany the arteries and end ultimately in the thoracic duct. Hence, carcinoma can spread (1) to the liver (2), to the pelvis by retroperitoneal lymphatics and (3) to the rest of the body by veins and by the thoracic duct.

Innervation

Autonomic nerve plexuses, submucosal and myenteric, differentiate from the neural crest. The stomach receives innervation from several sources: (1) sympathetic fibres are derived from preganglionic

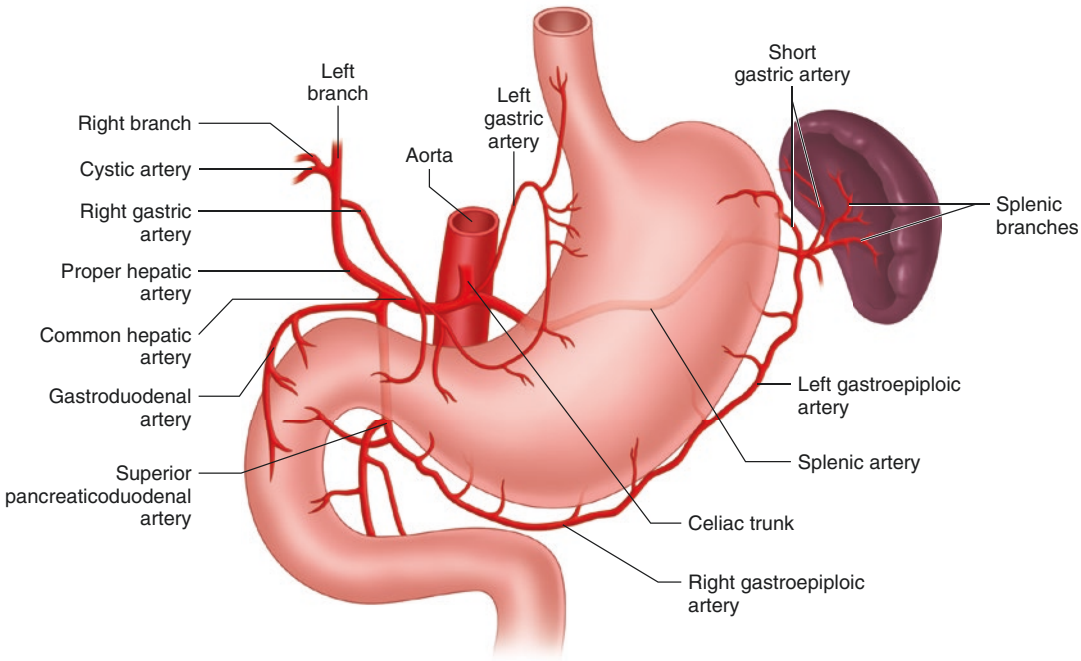

Fig. 110.7 Blood supply to the stomach

fibres arising predominantly from T6 to T8 spinal nerves, via the splanchnic nerves and celiac ganglion (synapse) supply blood vessels and musculature; (2) parasympathetic fibres from the medulla travel in the right and left vagus nerves, which form the distal oesophageal plexus, and (3) sensory vagal fibres include those concerned with gastric secretion. Both vagal nerves give rise to multiple gastric branches to the stomach wall, where the preganglionic fibres synapse with the ganglion cells in the submucosal (Meissner's) and myenteric (Auerbach's) plexuses. From these plexuses, postganglionic fibres are distributed to secretory components including cells and glands and to motor components such as muscle [10].

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Normal and Pathologic Mucosa

111

Marta C. Cohen

Normal Mucosa

The four regions of the stomach are the cardia, fundus, body, and antrum. Throughout the stomach, the wall is organized in four layers: mucosa, submucosa, muscularis propria, and serosa.

The gastric mucosa has a superficial layer of columnar mucus-secreting cells that contains foveolae (pits) where deep-seated coiled glands open (Fig. 111.1) [25]. The foveolae, also lined by the superficial columnar mucus-secreting cells, correspond to invaginations of the surface epithelium. They are wider in the antral mucosa (proximal to the pylorus) where at times adopt a slightly villous appearance (Fig. 111.2).

The columnar cells from the superficial mucosa depict basal located nuclei with an inconspicuous nucleoli and clear apical cytoplasm that contain neutral mucins which are positive with periodic acid-Schiff (PAS) stain [13, 14, 25]. The coiled glands are immersed in the loose connective tissue that constitutes the lamina propria, which extends between the muscularis mucosae and the more superficial foveolae.

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In the different areas of the stomach, the foveolae show subtle different features, and the deep glands diverge in function and histological appearance:

Cardia

This is the most proximal anatomic region of the stomach. It is situated immediately distal to the esophagus and is characterized by the presence of mucinous surface epithelium with underlying mucus-type or mixed mucus/oxyntic-type glands (Fig. 111.3) [19]. Traditionally, the cardia has been described as a 1–2-cm normal structure present at birth and with no definite anatomical limit with the gastric body [13]. However, it has recently been proposed that while the normal anatomic cardia may be comprised of pure oxyntic-type mucosa, the mucus-type glands develop as a metaplastic event and are an histologic manifestation of gastroesophageal reflux [4–7]. However, studies conducted in pediatric patients and our own experience show that cardia mucosa is frequently present in the proximal stomach with underlying loosely packed pure mucus-type or mixed mucus/oxyntic-type glands [11, 14, 19]. The mucus-type glands occupy approximately one half of the mucosal thickness and secrete predominately neutral mucin with a minimal quantity of sialomucins (Fig. 111.4) [13, 18, 25]. Although the cardia glands can

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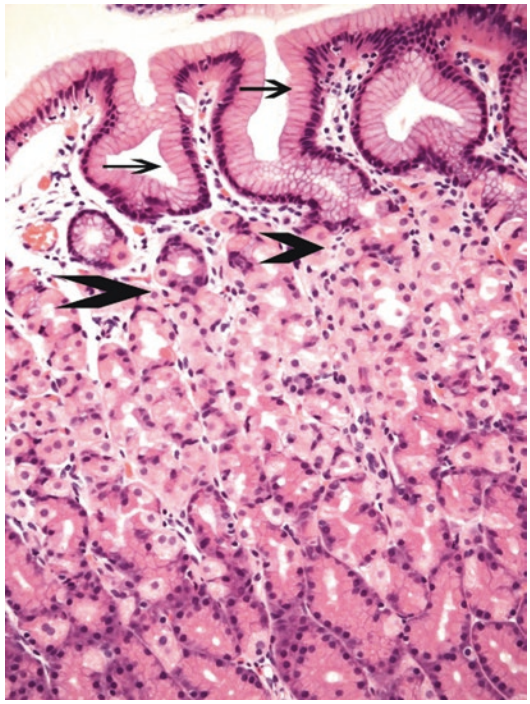

Fig. 111.1 Normal fundic-type gastric mucosa depicting a superficial layer of columnar mucus-secreting cells containing foveolae (*arrow*) where deep-seated glands open (*arrow head*) (H & E × 20)

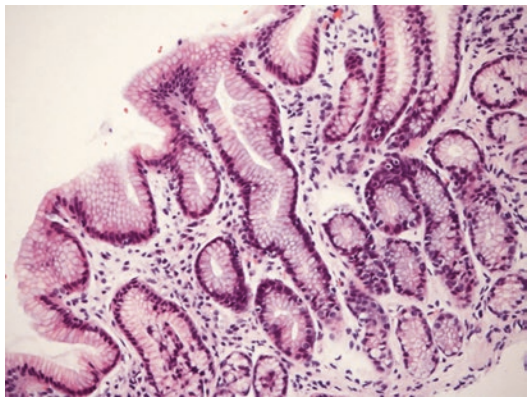

Fig. 111.2 The foveolae (pits) are wider in the antral mucosa (proximal to the pylorus) where at times adopts a slightly villous appearance (H & E × 10)

occasionally contain parietal cells, they do not usually include chief cells [14]. A rather unusual finding is the presence of ectopic intestinal mucosa or pancreatic acinar tissue in the cardia, described in a small percentage of infant postmortem examinations [14].

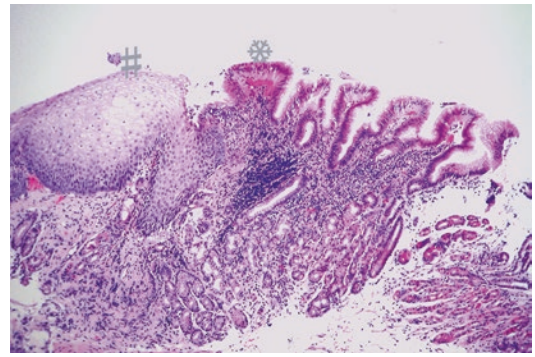

Fig. 111.3 The gastric cardia, situated immediately distal to the nonkeratinizing squamous mucosa of the esophagus (#), is characterized by the presence of mucinous surface epithelium with underlying mucus-type or mixed mucus/oxyntic-type glands (*) (H & E × 10)

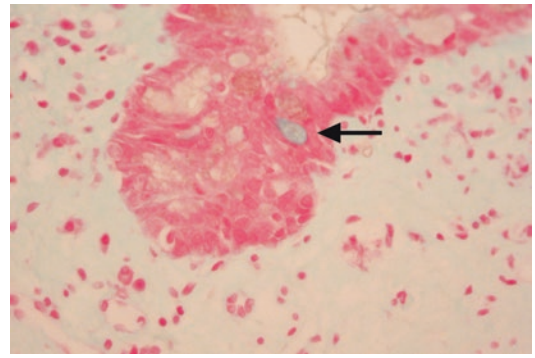

Fig. 111.4 The cardiac mucus glands secrete predominately neutral mucin with a minimal quantity of sialomucins (*arrow*) (Alcian blue pH 2.5 stain, × 40)

The different views expressed by adult and pediatric pathologists regarding the existence or not of the cardia-type mucosa could be explained by the inverse correlation between age and length of cardiac mucosa ($p = 0.005$) [11].

Fundus

The gastric fundus corresponds to that part of the body (corpus) that is adjacent to the cardia and bulges above it [14]. In comparison with the slightly villiform feature of the cardia and antral mucosa In comparison with the slightly villiform features of the cardia (Fig. 111.3 and 4) and antral mucosa (Fig. 111.2), the fundic foveolae (Fig. 111.1) appear, the fundic foveolae appear more flat,

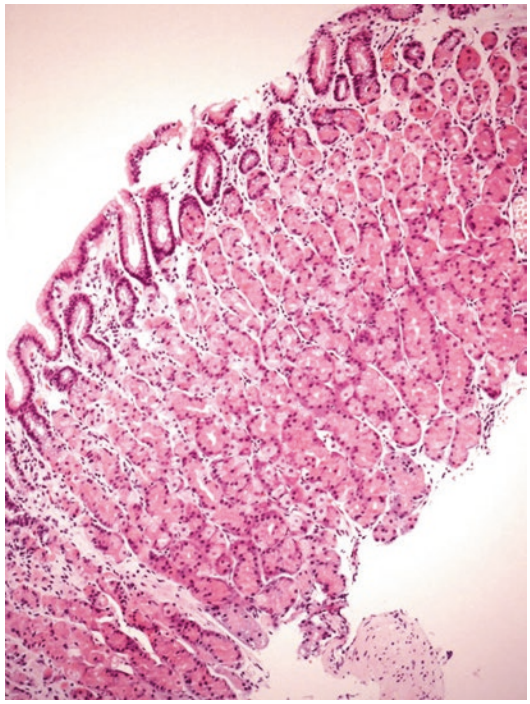

Fig. 111.5 Histology depicting rather flat fundic foveolae covering tightly packed acid-secreting glands (H & E × 10)

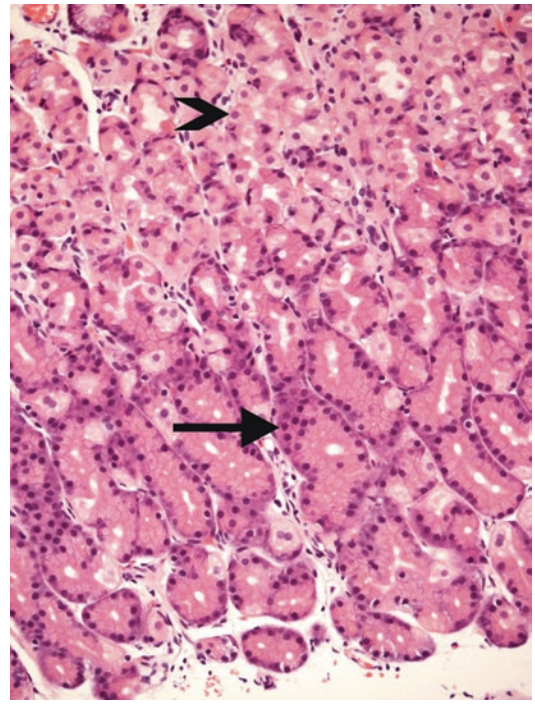

Fig. 111.6 Fundic glands are composed of bluish cuboidal chief cells (*arrow*), mucus cells, and pink parietal cells (*arrow head*) (H & E × 20)

making up less than 25% of the total mucosal thickness. The glands are tightly packed and straight rather than coiled (Fig. 111.5) [25]. They are composed of bluish cuboidal chief cells basally: chief, parietal, and mucus cells in the neck; and pink triangular parietal cells in the area corresponding to the isthmus of the gland (Fig. 111.6) [13]. The cellular products are inherent to each type of cell: chief cells secrete pepsinogen, parietal cells secrete acid, and mucus neck cells produce neutral and acidic mucin (in particular sialomucin) [25].

In addition to the above-described cell types, the fundic mucosa contains a variety of endocrine cells, mainly histamine-secreting enterochromaffin-like cells, although also serotonin enterochromaffin cells are also seen. The neuroendocrine cells are mostly located toward the base of the glands. Special stains (i.e., Grimelius) have now been replaced by immunohistochemical techniques (i.e., chromogranin, synaptophysin) to demonstrate the endocrine cells, not visible with routine hematoxylin and eosin stains. More sophisticated immunohistochemical techniques currently allow to identify specific hormones (i.e., gastrin or somatostatin) [25].

Body

The body or corpus makes up the majority of the stomach [13]. The mucosa of the body is identical to the mucosa of the fundus (see above).

Antrum

The antrum occupies the distal third of the stomach, extending between the incisura angularis and the pylorus. The foveolae (pits) occupy approximately half of the total mucosal thickness and may appear villiform (Fig. 111.2). The glands are mucus secreting, similar to the cardiac zone. Occasional parietal cells, but not chief cells, can be found at the junction with the adjacent body (fundic-type mucosa). As in the

fundus, the prepyloric antral mucosa contains endocrine cells that produce gastrin, enterochromaffin, somatostatin, and serotonin.

Lamina Propria

The collagenous tissue that provides support to the foveolae and glands constitutes the lamina propria. Elastic, reticulin, and occasional smooth muscle fibers as well as capillaries, arterioles, and nonmyelinated nerve fibers also contribute to the structure of the lamina propria [25]. During childhood, the lamina propria contains few lymphocytes, plasma cells, and rare eosinophils that do not expand the interglandular region (Fig. 111.7). B and T cell lymphocytes are scattered through the mucosa, and superficial aggregates are not usually seen. On the contrary, plasma cells (usually IgA-secreting type) often occur in small clusters [13]. Small lymphoid aggregates, devoid of germinal centers, can be rarely identified at the deepest part of the gastric mucosa.

Pathologic Mucosa

A detailed description of the histological characterization of various conditions presenting with an abnormal gastric mucosa is beyond the scope of this chapter.

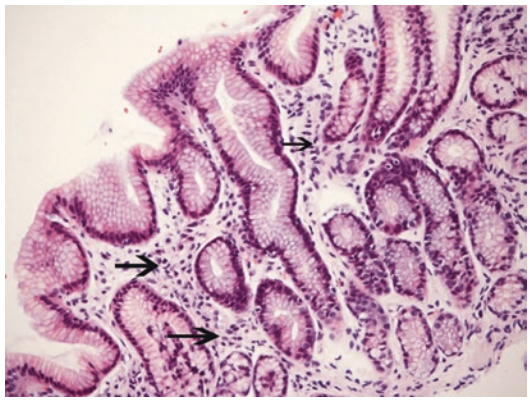

Fig. 111.7 Antral mucosa showing mucus glands immersed in the lamina propria; this contains few lymphocytes and plasma cells (*arrows*) (H & E × 10)

The term gastritis is used to denote inflammation-associated mucosal injury. However, epithelial cell injury and regeneration are not always accompanied by mucosal inflammation (i.e., chemical gastritis). Gastritis has a wide pathologic spectrum and anatomic distribution, as well as an evolving etiology. Different classification systems are in use. Key to the gastroenterologist and pathologist's collaborative work is a mutually understood and agreed classification [13, 14]. The Sydney pathologic classification of gastritis, published in 1990 and revised in 1994, is based on topography, morphology, and etiology of the inflammation [15]. The updated version of the Sydney System retained the general principles and grading of gastritis but provided with a useful visual analogue scale to help in the histological grading of gastritis. Although designed for gastritis in adults, the system has demonstrated that it applies to children as well [9].

According to the inflammatory cell infiltrates present in the gastric mucosa, the gastritis can be classified into acute or chronic forms. Chronic gastritis can further be subclassified as non-atrophic and atrophic and special types as chemical, radiation, lymphocytic, noninfectious, eosinophilic, reactive gastropathy (nonsteroidal anti-inflammatory drugs, bile reflux), etc. See Table 111.1.

The most usual entities encountered by the pediatric pathologist include, but are not limited to:

(a) *Helicobacter pylori* gastritis
(b) Lymphocytic gastritis
(c) Granulomatous gastritis and gastric Crohn's disease
(d) Eosinophilic gastritis
(e) Graft-versus-host disease
(f) Reactive gastropathy
(g) Nonspecific gastritis

Helicobacter pylori Gastritis

H. pylori infections have been associated with chronic gastritis, gastric and duodenal ulcer, and a higher risk of gastric carcinoma and gastric mucosa-associated lymphoid tissue (MALT) lymphoma. Diagnosis of *H. pylori* involves endoscopy with biopsy, culture, urease test, urea breath test, polymerase chain reaction (PCR),

and serologic detection of antibodies. However, the gold standard is the histologic detection of *H. pylori* in biopsy. *H. pylori* gastritis is infrequently biopsied in the acute phase of the infection. If performed, the histology shows mucosal injury with acute inflammatory cell infiltrates constituted by polymorphonuclear neutrophils. More commonly, the biopsy shows a chronic gastritis. *H. pylori* organisms present as coccoid and curved Gram-negative bacillus and are found particularly within the mucous lining of the surface epithelium. *H. pylori* are visible with hematoxylin and eosin (Fig. 111.8). The use of special stains such as silver stains (i.e., Warthin-Starry, Steiner), Giemsa or immunoperoxidase against

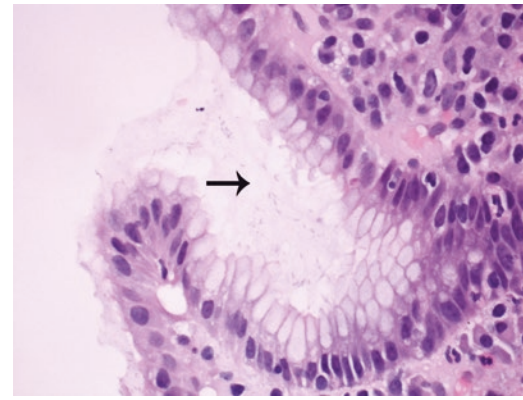

Fig. 111.8 Microphotography showing curved *H. pylori* organisms (*arrow*) of approximately 4 μ embedded within the mucus lining of the surface epithelium (H & E × 40)

Table 111.1 Etiologic-pathogenic classification of pediatric gastritis

Pattern of gastritis	Condition	
Infectious	Bacteria:	*Helicobacter pylori*
		Helicobacter heilmannii
		Streptococcus
		Staphylococcus
		Mycobacterium tuberculosis
		Treponema pallidum
	Fungi	*Candida albicans*
	Parasites	*Giardia lamblia*
	Virus	Cytomegalovirus
		Herpes
Noninfectious immune	Celiac disease	
	Graft-versus-host disease	
	Eosinophilic gastritis	
	Autoimmune gastritis	
	Henoch-Schönlein's disease	
	Polyarteritis nodosa	
Genetic/metabolic disorders	Cobalamin C disease	
	Chronic granulomatous disease	
Chemical/toxin injury	Nonsteroidal anti-inflammatory drugs (NSAIDs)	
	Other drugs	
	Bile reflux	
Physical agent injury	Tubes	
	Radiation	
Vascular	Congestion	
	Portal hypertension	
Unknown/uncertain	Crohn's disease	
	Ulcerative colitis	
	Ménétrier's disease (not associated with cytomegalovirus infection)	
	Non specific chronic gastritis	

From: Dimmick et al. [13, 14]

H. pylori is used when the organisms are difficult to identify with hematoxylin and eosin (Fig. 111.9). In children, *H. pylori* is a pangastritis, although the antrum and the cardia are usually more severely inflamed. Histologically, the lamina propria exhibits lymphoid and plasma cell inflammatory infiltrates which include a variable number of polymorphonuclear neutrophils (Fig. 111.10a) [1, 10, 15]. Usually, the pathologist encounters that the neutrophilic infiltrates involve the germinative area at the necks of the glands, constituting an "active" *H. pylori* chronic gastritis (Fig. 111.10b) [1]. Lymphoid follicles are fairly common at this stage. These are responsible for the nodularity of the gastric mucosa seen at endoscopy (Fig. 111.10c) [28]. Lymphoid hyperplasia and nodular gastritis appear to be more frequent in children than in adults and usually regress following *H. pylori* eradication [30].

Focal loss of glandular units, replaced by dense collagen bundles with scant inflammatory cells, has been described in treated long-standing *H. pylori* chronic gastritis [10]. The fibrous tissue is arranged in a "starry" shape, with a central area of scarring extending into the adjacent interglandular tissue. This feature could represent a very early stage of the atrophic gastritis described in some adult patients with *H. pylori*-associated chronic gastritis [2, 23]. In addition, the presence of isolated cells containing sulfated mucosubstances has been identified in gastric biopsies from pediatric patients with *H. pylori*-associated chronic gastritis.

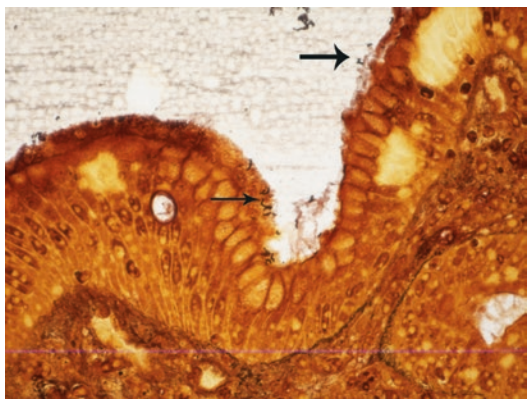

Fig. 111.9 *H. pylori* organisms positive with Warthin-Starry stain (*arrows*) (Warthin-Starry stain × 40

The presence of sulfated mucosubstances in patients with long-standing *H. pylori*-associated chronic gastritis, not present in the normal gastric mucosa, may represent a very early (perhaps reversible) stage of intestinal metaplasia [8].

Lymphocytic Gastritis

Lymphocytic gastritis is associated with *Helicobacter pylori* infection and with celiac disease. Initially described by Haot et al. [21], it is characterized by the presence of increased mucosal T cell lymphocytes both in the lamina propria as well as the surface and foveolar epithelium of the antrum and body with sparing of the deep glandular epithelium (Fig. 111.11a, b) [16, 21]. The number of intraepithelial lymphocytes in lymphocytic gastritis is 25 lymphocytes per 100 epithelial cells, although usually 30–65 lymphocytes per 100 epithelial cells are seen [34]. Children with lymphocytic gastritis and celiac disease had a mean of 40.64 lymphocytes per 100 epithelial cells [12]. There is no correlation between the histologic and clinical severity of lymphocytic gastritis in celiac disease, but the mucosa returns to normal with gluten withdrawal [14, 22]. In addition lymphocytic gastritis characterizes the endoscopic entity chronic varioliform gastritis. Of the patients with lymphocytic gastritis and celiac disease studied by DeGiacomo [12], only one had the endoscopic appearance of varioliform gastritis.

Granulomatous Gastritis and Gastric Crohn's Disease

Granulomatous gastritis may accompany systemic disease, infections, foreign body reaction, malignancy, or vasculitis but may also be an isolated finding [29]. In children, Crohn's disease is the most common type of granulomatous gastritis [13, 29]. Although histologic abnormalities are seen in up to 80 % of children with Crohn's disease, specific features such us giant cells are seen in approximately 30 % of cases [16]. Interestingly, histologic evidence of Crohn's disease may be found in absence of symptoms of inflammatory bowel disease or preceding them [16]. Histologic features of Crohn's disease include nonspecific chronic gastritis, chronic active gastritis, and the

more typical noncaseating giant cells granulomas (Fig. 111.12). A recent investigation conducted in children with inflammatory bowel disease indicated that although the presence of granulomas can support a diagnosis of Crohn's disease, severe inflammation and other abnormalities can occur in the proximal gastrointestinal tract either in Crohn's disease or ulcerative colitis [32].

In addition to the more convincing noncaseating giant cell granulomas, the presence of the so-called focally enhanced gastritis was initially considered to aid in establishing the diagnosis of Crohn's disease [24]. However, a retrospective case-controlled investigation conducted in children with inflammatory bowel disease, *Helicobacter pylori* and controls, showed that focally enhanced gastritis was present in 65.1 % of children with Crohn's disease, 20.8 % with ulcerative gastritis, 2.3 % controls, and 2.6 % children with *H. pylori* infection [31]. Focally enhanced gastritis characterizes by the presence of inflammatory cell

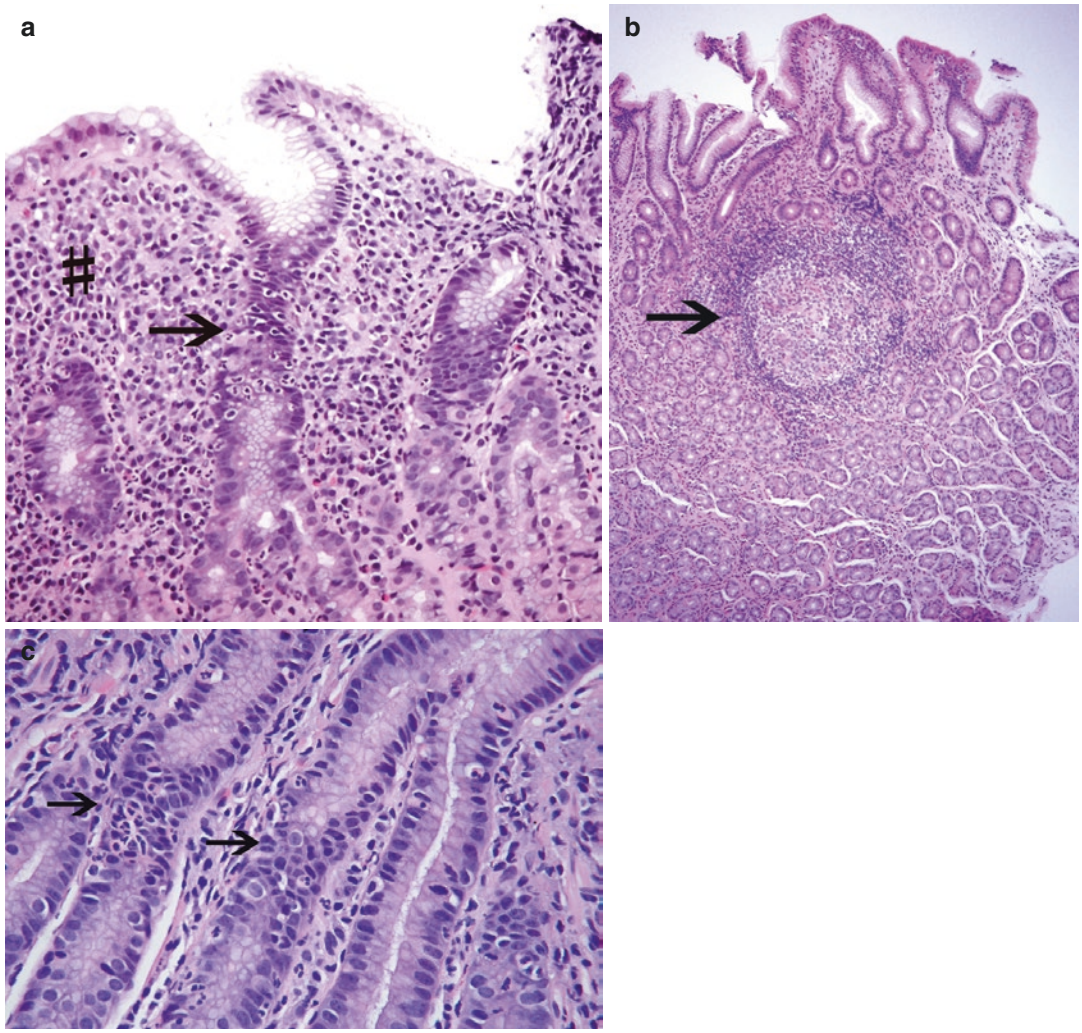

Fig. 111.10 (**a**) Antral mucosa depicting acute and chronic inflammatory cell infiltrates within the lamina propria (#) and invading the glandular necks (*arrow*) (H & E × 20); (**b**) higher magnification of glandular necks at the cardia showing neutrophilic infiltrates (*arrows*) which define an active gastritis (H & E × 40); (**c**) antral mucosa showing superficially located lymphoid follicles (*arrow*); these are responsible for the nodular appearance of the gastric mucosa at endoscopy (H & E × 20)

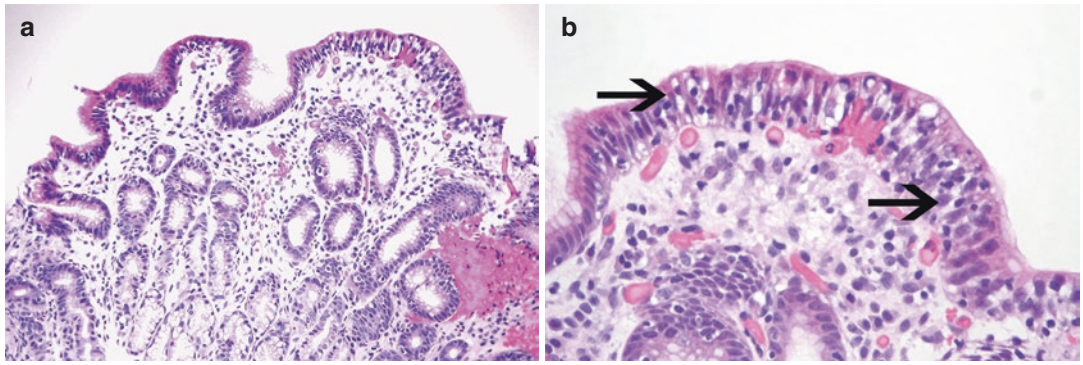

Fig. 111.11 (**a**) Patchy lymphocytic infiltration of superficial and foveolar epithelium which spares deep glands in a child with celiac disease (H & E × 20); (**b**) higher magnification of intraepithelial T cell lymphocytic infiltrates (*arrows*) (H & E × 40)

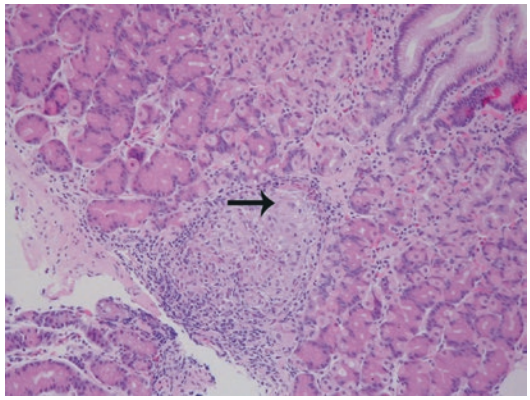

Fig. 111.12 Fundic-type gastric mucosa depicting non-caseating granulomas in a patient with Crohn's disease. The *arrow points* toward a giant cell (H & E × 20)

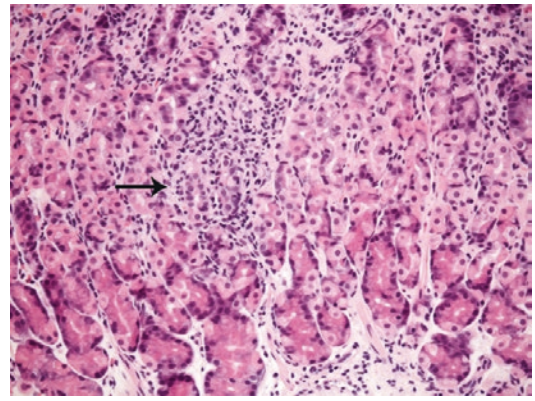

Fig. 111.13 Gastric biopsy in a child with Crohn's disease showing lymphoid inflammatory cell infiltrates surrounding fundic glands, constituting the so-called focally enhanced area of gastritis (*arrow*) (H & E × 20)

infiltrates (lymphocytes, mononuclear cells, and occasional neutrophils) surrounding a gastric foveola/gland or a small group of foveolae/glands (Fig. 111.13) [24].

With the exception of chronic granulomatous disease, other granulomatous gastritides are rare in children. These include sarcoidosis, Whipple disease, and vasculitis-associated and unclassifiable granulomas [13, 17]. Chronic granulomatous disease is an X-linked recessive immunodeficiency disorder occurring in boys, in which granulomatous gastric wall involvement is common [16]. The histological findings include presence of focal, chronic active inflammation in the antrum with granulomata, eosinophils, foci of necrosis, or giant cells. In my limited experience and that of other authors [14], pigmented histiocytes are not visualized.

Eosinophilic Gastritis

This is the gastric component of the eosinophilic gastroenteritis. The inflammatory cell infiltrate is mainly constituted by eosinophils involving the mucosa and submucosa, muscularis propria, and/or serosa of the stomach. Eosinophilic gastritis can be associated to food allergy, collagen vascular diseases, parasites, collagenous colitis, *H. pylori*, and idiopathic etiology [3, 14, 16].

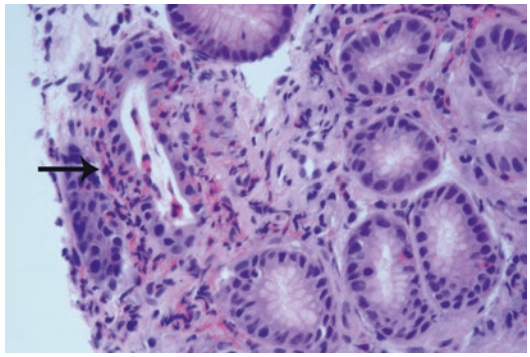

Fig. 111.14 Antral mucosa in a case of eosinophilic gastritis showing numerous eosinophils within the lamina propria and invading the adjacent glandular epithelium (*arrow*). (H & E × 40)

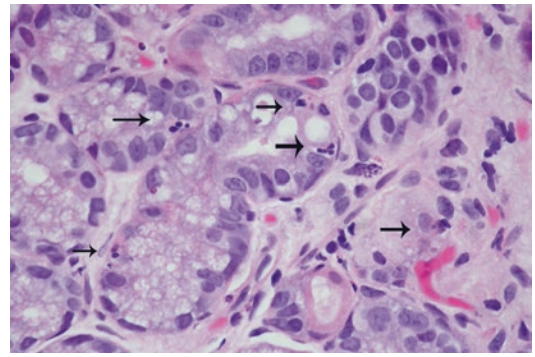

Fig. 111.15 Deep-seated glands in gastric antral mucosa depicting frequent apoptotic cells (*arrows*) in a case of graft-versus-host disease (H & E × 40)

Biopsies depict high number of eosinophils with fewer lymphocytes, plasma cells, and eosinophils within the lamina propria, with variable presence of mucosal necrosis and regenerative changes [14]. In allergic gastritis, the antrum is more commonly affected [20]. The histology depicts prominent infiltration of eosinophils within the lamina propria and invading the surface and foveolar epithelium (Fig. 111.14). Other inflammatory cell types included are lymphocytes, plasma cells, and neutrophils [13].

Graft-Versus-Host Disease

Graft-versus-host disease (GVHD), a common complication of hematopoietic stem cell transplantation, is a clinical syndrome that requires synthesis of clinical, laboratory, and histopathologic findings for diagnosis [33]. Histological features of early GVHD include crypt epithelial apoptosis and dropout and variable lymphocytic infiltrate within the superficial epithelium and lamina propria (Fig. 111.15). The features can be focal and subtle or more diffuse and severe, including crypt necrosis and denudation of areas of the superficial mucosa [27].

Reactive Gastropathy

The mucosal changes that characterize the chemical or reactive gastropathy are the presence of foveolar hyperplasia, reduced secretion of mucins, edema, vascular ectasia, and strands of smooth muscle in the lamina propria associated with minimal or absent inflammatory cells in the antral mucosa (Fig. 111.16) [14, 26]. The most frequent etiologies of reactive gastropathy in children are duodenal-gastric bile reflux and nonsteroidal anti-inflammatory drugs.

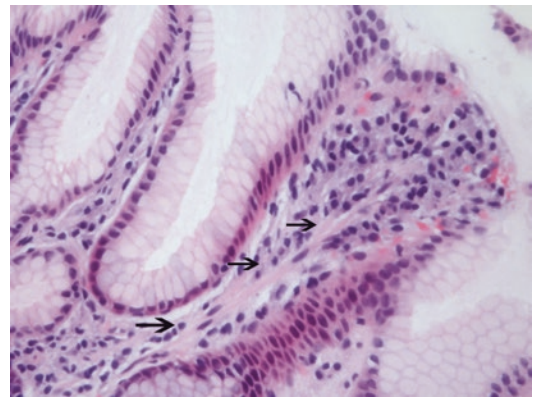

Fig. 111.16 Reactive gastropathy characterizes by foveolar hyperplasia, presence of strands of smooth muscle in the superficial lamina propria (*arrows*), and absence or minimal inflammation in the antral mucosa (H & E × 20)

Nonspecific Gastritis

A significant number of children present with chronic gastritis, usually of mild or moderate severity, for which no cause is identified. The inflammation is chronic with lymphocytes and plasma cells, usually patchy and more superficial than deep [13, 16]

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Part XX

Evaluation

Upper GI Endoscopy in the Diagnosis of Gastropathy

112

Mike Thomson

There is clearly no substitute for visual diagnosis reinforced by histological biopsy assessment in the diagnosis of mucosal pathology involving the stomach in children. The inflammatory pathologies which cause symptoms are amenable to diagnosis and differentiation with this tool, and anatomical abnormalities can also be identified. A distinction between "gastropathy," which is the term used for description of visual abnormalities at endoscopy involving the stomach (and encompassing histological pathologies), should be made in contrast to the term "gastritis," which is taken to indicate histological inflammation. In other words "gastritis" is a term that should not be used by the endoscopist to describe their *macroscopic* determination of pathology as this is a *microscopic* diagnosis. This important distinction is elegantly drawn by [1].

More detailed reviews of infant gastropathology and technology can be seen in other texts [2].

This chapter will not deal with histological diagnoses, which are dealt with in detail in Chap. 111. Rather it will describe the process, tools, ideal environment, methodology, and macroscopic diagnoses which are required by, and attributable to, upper GI endoscopy in children. More extensive detailed expositions on pediatric endoscopy in general are available [3, 4].

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Process

Clearly the first issue is to make a decision that gastroscopy as part of an upper GI endoscopic assessment will be an investigation in an individual child that will actually alter patient management. Symptoms of gastric pathology may be indistinguishable from that arising from the esophagus or duodenum, e.g., dyspepsia, nausea, and regurgitation. In this scenario examination of the upper GI tract may be of advantage in differentiation of the origin of the symptom and hence directing appropriate management. Symptoms and their origin are examined in other parts of this book. Once the decision is made to proceed to EGD, then the child and family should have adequate information made available to them, with the possibility of reflection on the decision to move ahead to EGD available. Leaflets, a web presence, endoscopy unit visits, and face-to-face explanations are obvious ways for these issues to be addressed, and consent from parent and, if needed or desired, child would then be "informed" consent. All parts of this patient's journey should be subject to examination in training.

Ideally the unit would be close to, or part of, a pediatric ward, although not unreasonably endoscopy units may exist within a theater complex; occasionally, although certainly less than ideal, the existence of a unit is within a larger adult endoscopy facility. Recovery facilities may, and probably should, preclude such an arrangement.

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Age-appropriate material with cartoons, videos, and distraction by play therapists and concealment of any potentially scary equipment may make the initial impression less than forbidding for the child. Age-appropriate interaction with the child is the most important strand however. Excessive noise from adjacent rooms, protection of privacy, adjustable temperature, and lighting are all common sense measures which do not need to be reiterated here.

The recovery area would also be child-friendly and equipped with resuscitation equipment.

Clean and dirty areas for scope processing are considered mandatory nowadays with through-the-hatch-type processors, and guidance for setting up such an area is freely available in most countries by visiting websites such as that of the British Society of Gastroenterology (www.bsg.co.uk).

GI endoscopy is an invasive procedure and in almost all children has the potential to cause great distress if performed without adequate sedation or general anesthesia. Unfortunately for some children, pediatric endoscopy is still sometimes performed without any or with minimal so-called conscious (although it rarely is so) sedation. Although there is an obvious need to alleviate distress in infants and children undergoing endoscopic procedures, there is no consensus on the best approach. The choice is between sedation and general anesthesia. The ideal sedative regimen would be effective for every patient, act rapidly, induce an adequate but safe levels of sedation for the duration of the procedure, wear off immediately afterward, and have no adverse effects. No such regimen exists. For this reason, many advocate the use of general anesthesia for pediatric endoscopy. Others disagree, arguing that sedation has an essential role in pediatric practice and that for GI endoscopy it can be both safe and effective. The logistic and financial implications of relying on general anesthesia must also be considered. The true morbidity and mortality rates associated with pediatric endoscopy, whether performed under general anesthesia or sedation, are unknown.

From a practical point of view, it is generally considered possible to distinguish between two distinct levels of CNS depression, referred to as "conscious sedation" and "deep sedation." The distinction between these states is central to the debate about safety and efficacy. The term conscious sedation implies a level of CNS depression in which communication is maintained so that the patient can respond to verbal command. The term deep sedation implies a level of CNS depression in which the patient is essentially unconscious and does not respond to verbal command. Practically it is rare that conscious sedation state is used in pediatric endoscopy, and therefore by any safety standards, it is recommended that one practitioner, usually a pediatric anesthesiologist, is dedicated to the safety of the child and administration of whatever method of deep sedation/GA is used. The mode of this is less important, i.e., safe airway, successful completion of procedure, no distress, timely execution, and ability of the endoscopist to concentrate on their responsibility of carrying out the procedure without having to worry about the child's safety; these are the important considerations [5–7].

Tools

Endoscopy and mucosal biopsy are a cornerstone of modern pediatric gastroenterology practice. The ability to make an accurate tissue diagnosis has been a major factor in the development of pediatric gastroenterology. Endoscopy continues to evolve, and in today's age, pediatric gastroenterologists are using the endoscope not only as a diagnostic device but increasingly as a therapeutic tool and vehicle by which to deliver endoluminal, and even extraluminal intraperitoneal, minimally invasive therapies, although these remain some way off. These are early days, but obvious initial benefits are saving procedure time, hospital admission time, and avoidance of surgical morbidity. In due course therefore the stomach may provide a portal to the peritoneum allowing natural orifice endoluminal therapeutic endoscopic surgery (NOTES) to occur. This is dealt with in Chap. 111, and its value is yet to be fully determined.

Evolution of Endoscopes

Internal examination of the human body dates back to Hippocrates (460–377 BC). He used a speculum for rectal examination, and in his treatise described rectal inflammation, hemorrhoids, and fistula. Abu Al-Qasim Khalaf ibn Abbas az Zahrawi (930–1013 AD), an eminent surgeon in Cordoba, Spain, ingeniously added a light source (reflected light by a glass mirror) for examination of the cervix. In 1806, Philipp Bozzini, a German physician from Frankfurt, invented the "lichtleiter" (light conductor) using the candle as source of illumination [8]. Visualization was limited; the examination was unfortunately painful to the patient. The Vienna Academy of Medicine did not view it kindly and reprimanded him for being "too curious." The French physician Antonin J. Desormeaux in 1858 resurrected Bozzini's invention and developed the "lichtleiter" further, replacing the candle by the much brighter gas flame using alcohol and turpentine as fuels [9].

Kussmaul performed the first esophagogastroscopy on a professional sword swallower. He swallowed a 47 cm long, 13 mm diameter metal tube. Unfortunately the Desormeaux lamp (gas illumination) had inadequate light failing to illuminate. To counter illumination problems, Leiter and Nitze used loops of platinum wire as filaments for electric lamps operated with galvanic batteries [10]. These lamps could get very hot, and in addition they devised a cooling mechanism for the hot light source eventually performing the first successful gastroscopy. They ended up arguing about the resulting credit, and historically they came to blows engaging in vitriolic correspondence. Leiter later collaborated with Johann von Mikulicz, successfully moving the light source to the distal end of the endoscope [11].

The first flexible gastroscope was invented by Dr Rudolph Schindler in 1932 [12]. The gastroscope was 75 cm long and 11 mm in diameter. About one third of the entire length of the tube toward the end could bend by an angle of 34° without distorting the image. A number of short focus lenses were positioned throughout the tube, and the light source was a miniature light bulb. This semiflexible gastroscope remained in popular use until 1957.

The fiberoptic era was born when, in the American gastroscopy society meeting of 1957, Hirschowitz successfully demonstrated the prototype, formulated with the help of a physicist [13]. In 1960 ACMI Ltd produced the first commercial fiberoptic gastroscope. Robert Kemp in 1962 suggested using a controllable directional tip helping to develop it further.

In 1983 the first digital endoscope was produced by Welch Allyn. At the tip was an electronic sensor consisting of packed grid of photocell receptors which electronically transmitted images to a video processor and then to a television monitor. This evolution has particularly accelerated the endoscopist's training, additionally adding to the interest of all present in the theater including the patient (Fig. 112.1).

The use of gastrointestinal endoscopy in the pediatric population was initially driven by the imperative of histological diagnosis in conditions such as celiac disease and the inflammatory bowel diseases. It has superseded such modalities as the Watson-Crosby capsule for obtaining small

Fig. 112.1 A Hirschowitz gastroscope recently (Nov, 2006) sold on eBay for 68.50

bowel mucosa and offers advantages over these methods by way of observation of the whole of the upper GI mucosal surface and anatomy while providing as many biopsies as are needed for diagnosis of esophagogastroduodenal pathology; indeed the duodenal biopsies provided have been shown to be as good as those obtained by capsule without the necessity for screening irradiation and usually occurring in a more controlled airway setting of general anesthetic [14].

The use of diagnostic GI endoscopy in children has followed developments in the adult sphere and is now considered standard practice for all mucosal GI diseases. Indeed modalities such as wireless capsule endoscopy and double balloon enteroscopy added to upper GI endoscopy and ileocolonoscopy now enable the pediatric endoscopist to visualize and biopsy the whole of the gut from mouth to anus [15–17].

The more recent advances of therapeutic intervention have transformed areas such as enteral nutrition support with PEG and PEJ tube insertion, esophageal stricture management, and especially variceal and non-variceal bleeding management and are now considered mandatory for any advanced pediatric endoscopist.

Technique of Endoscopy Involving the Stomach

The instrument will pass down the narrow confines of the esophagus without difficulty. It is important to make any necessary adjustments to keep the esophageal lumen at the center of view (Fig. 112.2). Insufflation of air from time to time will maintain a clear view. The gastroesophageal junction is identified using a number of anatomical features.

First, the z-line, or dentate line, of the gastroesophageal mucosal junction may be visible, the esophageal mucosa appearing pale compared with the salmon-pink gastric mucosa (Fig. 112.3).

Second, the gastric rugae may be seen immediately distal to the esophageal mucosa. Last, there may be an area of relative luminal narrowing at the level of the diaphragm, the "diaphragmatic pinch." Each of these indicators should be evaluated because in individual patients, some may be more reliable than others. A sliding hiatus hernia can be confirmed by noting that the z-line and gastric rugae lie above the diaphragmatic pinch (Fig. 112.4). Similarly, in patients with Barrett's esophagus, the z-line may be proximally displaced (Fig. 112.5). Finally, before advancing through the gastroesophageal junction, aspiration of air reduces the intraesophageal pressure and may reveal small esophageal varices

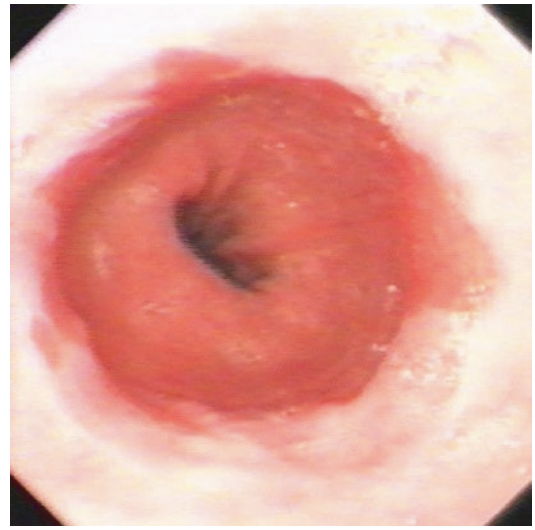

Fig. 112.2 Esophageal lumen

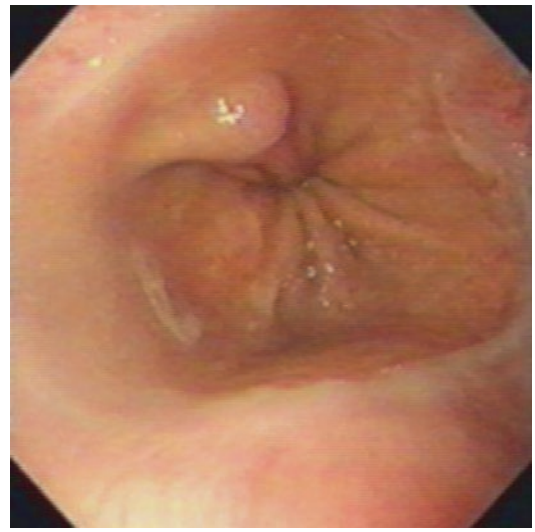

Fig. 112.3 Dentate or z-line, with an inflammatory polyp

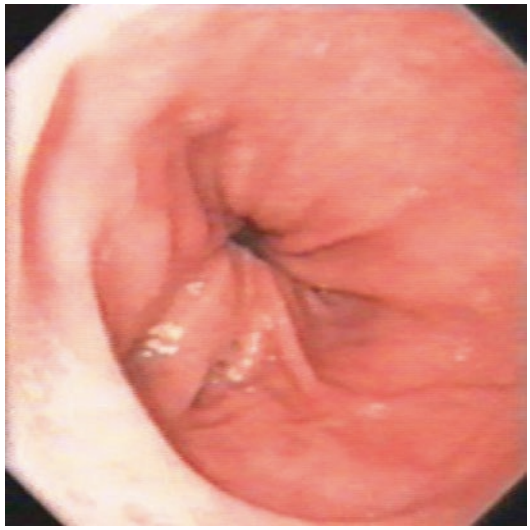

Fig. 112.4 Hiatus hernia showing diaphragmatic "pinch"

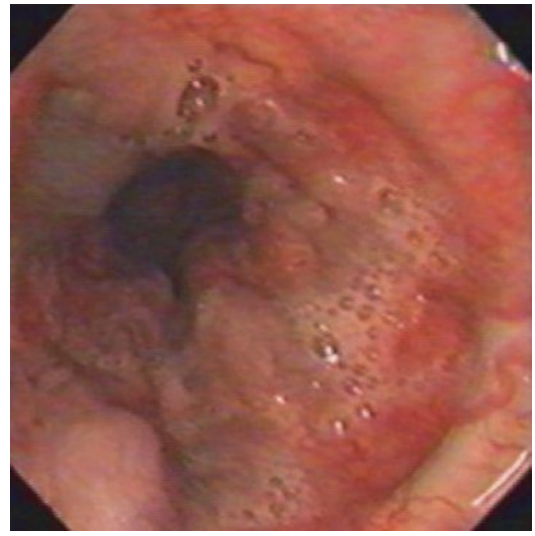

Fig. 112.6 Esophageal varices

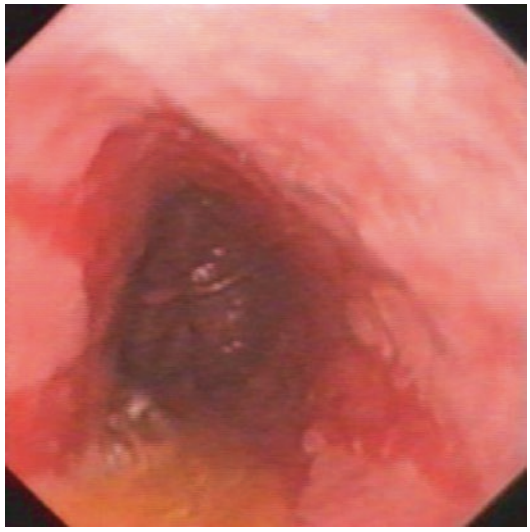

Fig. 112.5 Barrett's esophagus

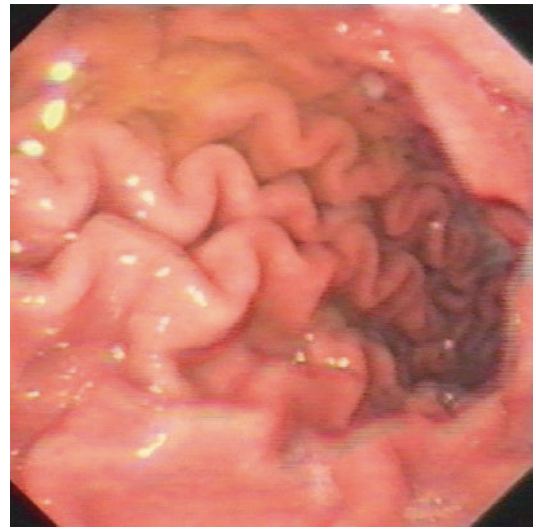

Fig. 112.7 Gastric rugae

that might not otherwise be obvious (Fig. 112.6). The endoscope moves easily through the gastroesophageal junction, but immediately upon entering the stomach, the forward view may be obscured by gastric mucosal folds in the cardia. At this point adequate insufflation of the stomach is necessary to gain a clear view. Aspiration of pooled gastric secretions is critical prior to full distension of the stomach to minimize the risk of aspiration. As air is insufflated, the gastric lumen and the gastric rugae are evident, but with further distention, the rugae gradually flatten (Figs. 112.7 and 112.8). As the endoscope is advanced, it readily slides down along the greater curvature of the stomach to the gastric antrum, facilitated by clockwise torque, advancement, and upward tip deflection. The lesser curvature may be seen on the right, and often the prominence of the area gastricae can be noted (Fig. 112.9). This is a normal mosaic appearance and finding, although

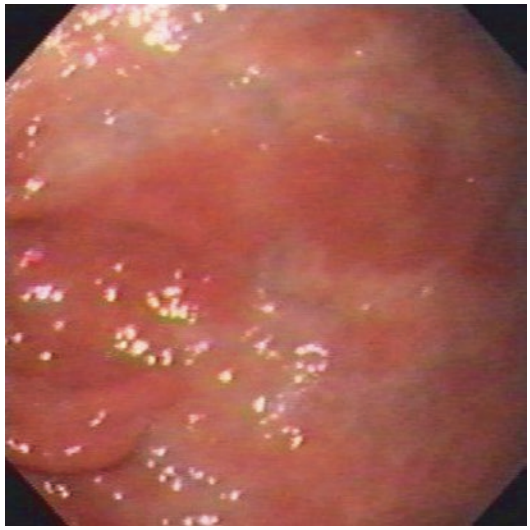

Fig. 112.8 Insufflation expands stomach and therefore rugae disappear

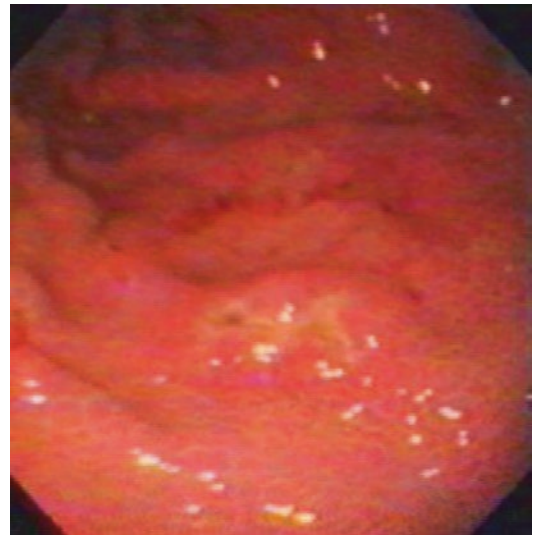

Fig. 112.10 Crohn's of stomach: mosaic appearance of edema

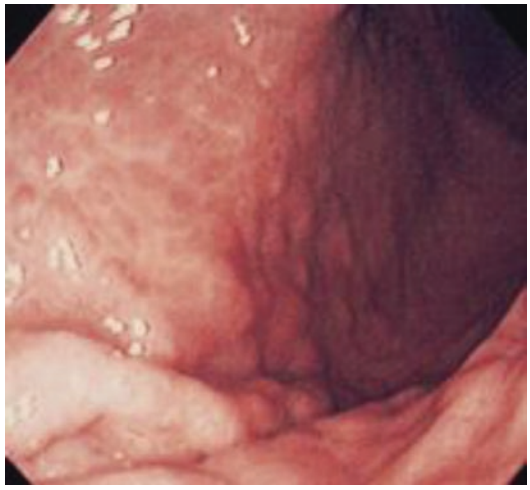

Fig. 112.9 "Area gastricae": prominent area on lesser curvature of stomach which is a normal finding

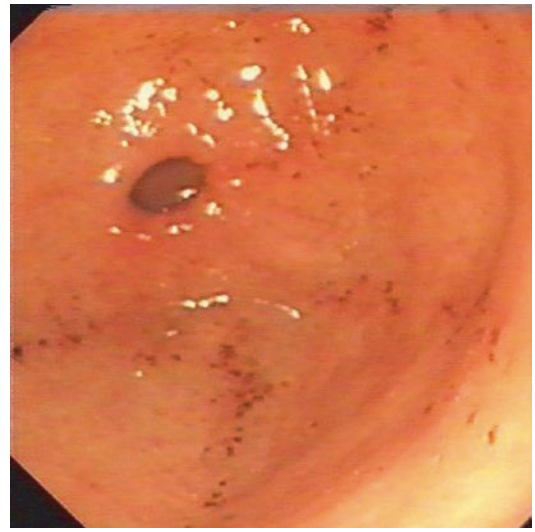

Fig. 112.11 Pylorus

if seen elsewhere in the stomach it can point to the possibility of inflammation such as Crohn's disease [18] (Fig. 112.10). Very often as the endoscope reaches the antrum, the pylorus comes into view (Fig. 112.11). However, in infants and small children, the pylorus is often located very close to the angulus incisura, and the angle of approach is necessarily somewhat acute (Fig. 112.12). In this case it can be very helpful to perform a so-called "J-maneuver" of the endoscope. The endoscope is retroflexed in order to look back up the stomach (thus adopting a "J" configuration). Then with some minor adjustments, it is usually easy to look face-on at the edge of the angulus incisura. The pylorus lies a few centimeters distal to the angulus. Once visualized with this maneuver, the line of approach is

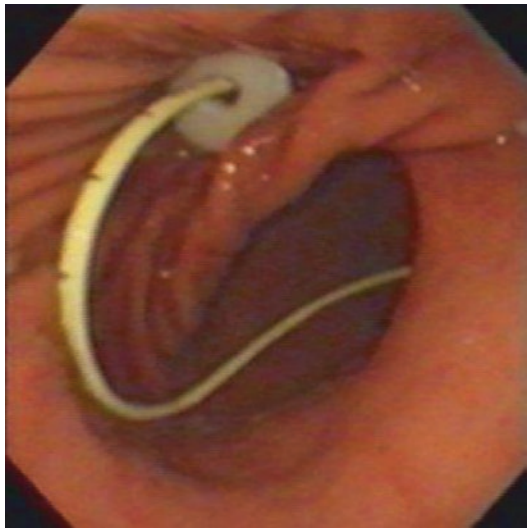

Fig. 112.12 Angula incisura around which a PEGJ tube has been passed into the pylorus

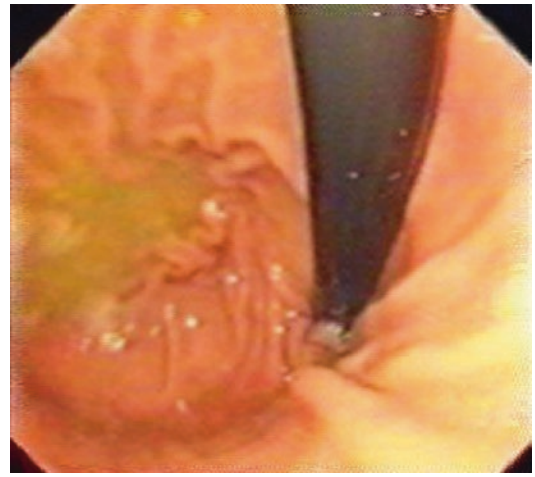

Fig. 112.13 J manuever to see the cardia and fundus

clear. The J-maneuver can also be very helpful in performing a thorough examination of the gastric fundus and cardia (Fig. 112.13). The gastric body lies proximal to the angulus and further proximally is the fundus and the gastroesophageal junction through which the shaft of the endoscope is to be seen passing downward (Fig. 112.13). If the endoscope is carefully withdrawn in the retroflexed position and some lateral and rotational adjustments are made, thorough examination of the entire gastric mucosa is possible.

Once the entrance to the pyloric canal is visualized, intubation is usually straightforward. If the pylorus is closed, it appears as a series of mucosal folds radiating from a central point. With gentle pressure, sometimes assisted by a brief puff of air, the endoscope will usually pass easily into the pylorus.

Biopsies are usually taken from the antrum which can be 2 or 4 in number, and this is the area with highest yield for *Helicobacter pylori*, and the body. A rapid urease test for *H. pylori* is also usually obtained. Some children have *H. pylori* identified in the fundus also. Any lesion should be photographed and if necessary biopsied. Gastric aspiration for identification of TB may be helpful. More recent innovations such as narrow band imaging, autofluorescence, and now confocal endomicroscopy with up to 1,000× magnification (i.e., histology in vivo) allow specific targeting of biopsies to areas likeliest to provide highest diagnostic yield [19] (Figs. 112.14, 112.15, 112.16, 112.17, and 112.18).

Diagnostic Indications

These are varied and are summarized in Table 112.1. Each pathology is identified and examined in more detail in the relevant chapter with description of macroscopic and histological appearances so this will not be undertaken here.

It is clear that the major impact over the last 20 years on identification of mucosal pathology and its potential symptomatic causation has been the endoscopic assessment and biopsy. Each pathology will not be dealt with here, but the reader is directed to the appropriate mucosal and symptom-specific chapter.

Therapeutic Endoscopy of the Stomach

These are summarized in Table 112.2, and as they are not dealt with elsewhere in the text, it will be touched upon here as follows.

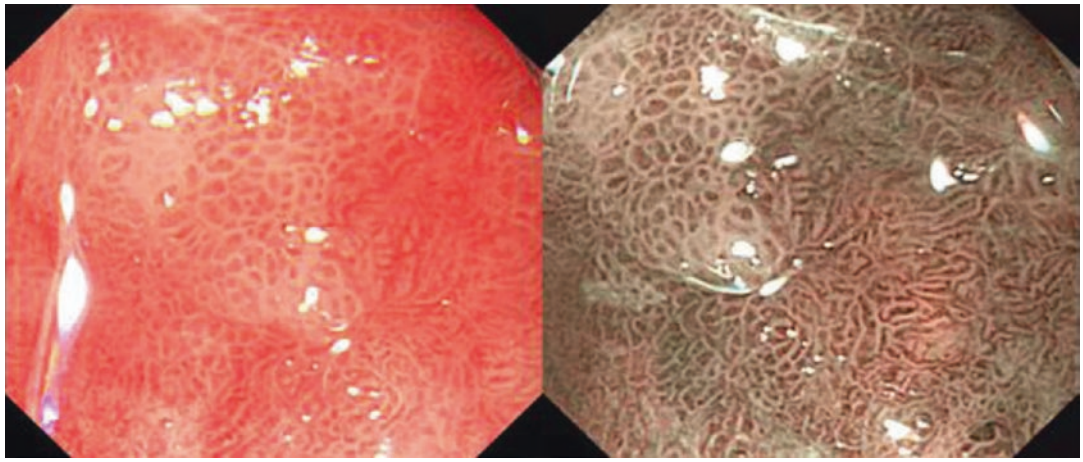

Fig. 112.14 Narrow band imaging (*right*)

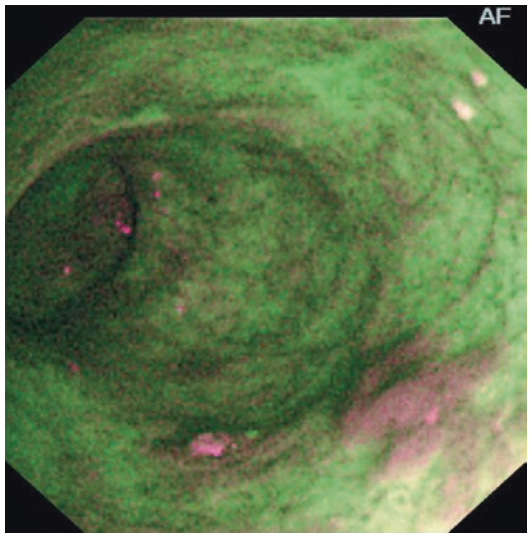

Fig. 112.15 Autofluorescent endoscopic imaging

Fig. 112.16 Tip of confocal endomicroscope revealing laser imaging portal

Gastric Bezoar

The term "bezoar" derives from the Persian word *badzehr*, which means antidote. Some types of trichobezoar are able to precipitate or bind arsenic compounds (a commonly used ingredient in the poison) hence acting as an antidote. In 1575, Ambroise Paré, a French army physician and surgeon, proved this to be wrong, an experiment which costs the cook his life. A cook at Paré's court was caught stealing fine silver cutlery who agreed to be poisoned. Despite using the bezoar stone, he died in agony days after. Paré had proved that the bezoar stone could not cure all poisons as was commonly believed at the time.

Bezoars are of several types with phytobezoars being the commonest type. These are soft and are composed of plant and vegetable fibers [20]. In comparison trichobezoars are composed of hair, undigested fat, and mucus. The hair may come from the patient, other humans, animals, carpet fibers, or blankets. Hair fibers are trapped

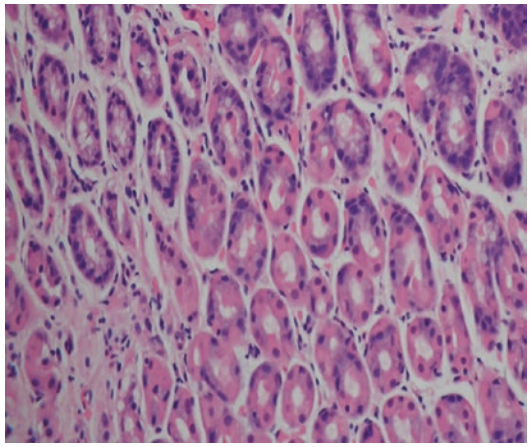

Fig. 112.17 Gastric histology "en face"

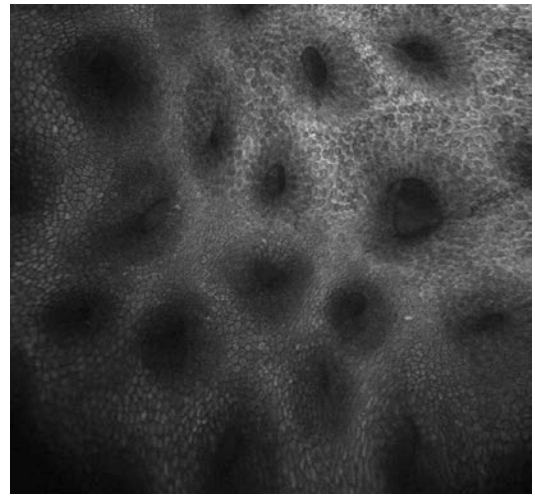

Fig. 112.18 Surface endo-histology of the stomach at confocal endomicroscopy

Table 112.1 EGD and diagnostic indications involving the stomach

Mucosal injury and inflammatory pathologies	Bleeding lesions	Miscellaneous
Acute (stress) ulceration	Acute (stress) ulceration	Bezoars
H pylori gastritis	Gastric fundal varices	Ectopic pancreas
H pylori gastric ulcer	Portal gastropathy	Adenomatous polyps (e.g., Gardner's and FAP)
NSAID gastritis	Dieulafoy's lesions	Hamartomatous polyps (Peutz-Jeghers polyposis)
Eosinophilic gastritis	*H. pylori* gastric ulceration	Gastric carcinoma, lymphoma, leiomyoma, leiomyosarcoma, mucosal-associated stromal tumor (MAST), GOJ tumors
GVHD	Virus-related hemorrhagic gastritis (esp. Influenza A)	GAVE (gastric-associated vascular ectasia or watermelon stomach)
Autoimmune gastritis	Drug-related gastritis	
Atrophic gastritis	GAVE (gastric antral vascular ectasia or watermelon stomach)	
Crohn's and UC-related gastritis		
Varioliform gastritis		

in gastric folds and resist peristalsis because they are slippery. More hair is added, and a ball forms. The hair protein is denatured by gastric acid, causing the ball to turn black. Fat becomes trapped in the hair fibers and ferments, leading to a putrid smell.

One variant of trichobezoars is the "Rapunzel syndrome." This is a trichobezoar extending from the stomach into the small intestine sometimes even involving entire length of the small intestine. The twisted hairs can become hard like a wire. There are reports in which these can cause compression of the mesenteric wall of the intestine occluding the blood supply resulting in pressure necrosis and perforations [21, 22] (Figs. 112.19, 112.20, and 112.21).

Endoscopy or surgery may be used to remove bezoars. With the help of an endoscope, these are broken into smaller pieces using a polypectomy snare, biopsy forceps, directed water jets [23],

Table 112.2 EGD and therapeutic indications involving the stomach

Gastric fundal variceal banding
Gastric fundal variceal histoacryl glue injection
Non-variceal bleeding lesion clip application, thermocoagulation, or argon plasma coagulation
Foreign body removal (esp. sharp objects and mercury or lithium batteries)
Percutaneous gastrostomy insertion
Percutaneous gastrojejunostomy insertion
Pancreatic cystogastrostomy
Pyloric balloon dilatation
Endo-pyloromyotomy with needle knife or tapered myotome
Botulinum toxin injection into pylorus
Pancreatic pseudocyst transgastric drainage
Polypectomy
Anti-obesity endotherapy
Notes

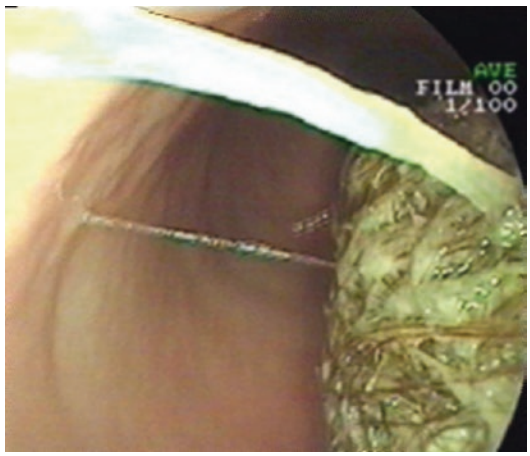

Fig. 112.19 Endoscopic view of the large gastroduodenal trichobezoar

injection of enzymes (papain, cellulose), or mechanical lithotripsy (bazotome, a needle knife device, or bezotriptor, a lithotriptor) [24]. Fifteen patients were treated with mechanical lithotripsy with a 100 % success rate (five patients required two sessions). Gastroscopy re-performed 3 days later showed only four patients with small residual bezoar fragments, which were removed endoscopically. Once the bezoar is broken into smaller pieces, these can then either be removed endoscopically or allowed to pass through the pylorus.

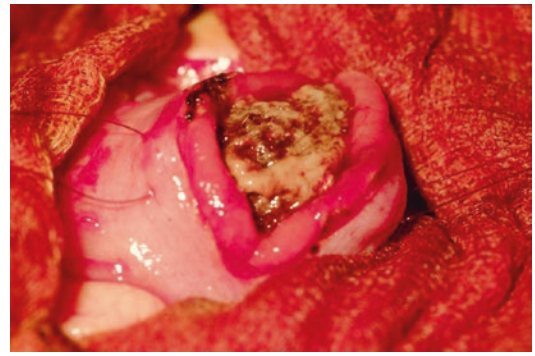

Fig. 112.20 Surgical removal of trichobezoar

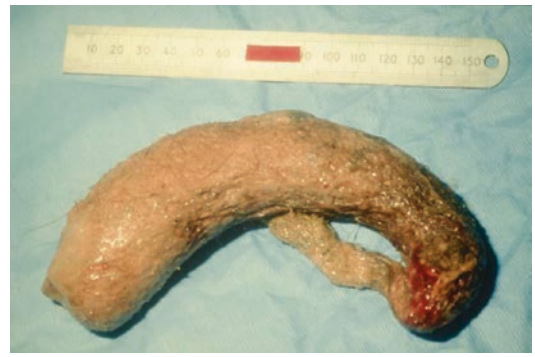

Fig. 112.21 Bezoar from an 11-year-old girl with Rapunzel syndrome. The large size (34 cm long and 8 cm in diameter) did not permit endoscopic removal

Another group has reported use of electrohydraulic lithotripsy (EHL) to treat bezoars [25]. After submerging the bezoar in saline, the EHL probe was brought into direct contact with the mass and used to deliver a series of short bursts that fragmented the bezoar into pieces 1–1.5 cm in diameter. Uncomplicated 100 % success (11 patients) was reported. In addition there was no recurrence after 30–68 months follow-up.

A group in China has reported use of a mini-explosive device to treat diospyrobezoars [26]. Hydrazoic acid (trizoic acid) is a colorless, volatile, and extremely explosive liquid at room temperature and pressure. All the salts are explosive and readily interact with the alkyl iodides. The metallic salts all crystallize in the anhydrous form and decompose on heating, leaving a residue of the pure metal. It is a weak acid (pKa 4.6–4.7). In this report trizoic lead was loaded into small steel tubes (0.5 cm thick, 1 cm in length, and 2 mm in

diameter). These were connected to a pulsed neodymium laser. The device was passed through the endoscope and placed in direct contact with the bezoar. The laser was ignited, followed by a mini-explosion and a small hole in the bezoar. After three to five of these explosions, bezoar fragments were then removed with a snare. Gastric mucosa was intact in all patients (except a small erosion in one patient). No discomfort was reported during the procedure, and 21/31 patients were cured in one treatment session. Patients reportedly felt no discomfort. This method with its hazards is unlikely to be adopted worldwide.

Coca-cola [27] was used in a 42-year-old man in four aliquots of 30 mls. Each aliquot was injected into the bezoar with the endoscope being forcefully buried into the bezoar at four different places. Thereafter the diet was restricted for 48 h. A repeat endoscopy showed the bezoar had cleared from the stomach.

Endoscopic Pyloromyotomy for Congenital Pyloric Stenosis

Ramstedt's pyloromyotomy (open and laparoscopic) has been the gold standard operation for treatment of congenital pyloric stenosis for more than 80 years. Recently Ibarguen-Secchia from Texas has reported use of endoscopic pyloromyotomy in a series of ten children [28]. Transendoscopic use of a needle knife or a sphincterotome was used in a quadrantic manner through the mucosa, and division of the internal hypertrophied circular muscle was carried out. Prior endo-ultrasound can help in the decision as to how deep to make the incision, but standard transabdominal ultrasound is sufficient. The route of treatment is somewhat more appropriate than dividing the serosa and outer normal longitudinal muscle as in the standard approach, and it has not seemed to matter that the mucosa is divided. This was performed with a view to achievement of a quicker operation and post-op recovery time. Nine out of ten children had the procedure as a day case, and one out of ten needed electrolyte correction before being treated the next day. All children were fed only after an hour of the procedure compared to the median time of 38 h for laparoscopic pyloromyotomy and 64 h for an open abdominal procedure. Vomiting continued to a lesser degree in two but eventually resolved in all over a 6–18-month follow-up. The results are impressive. However, this is only a one operator-conducted small case series; clearly, one needs to be cautious about bleeding and perforation, which may cause significant morbidity particularly in this younger age group (Figs. 112.22 and 112.23).

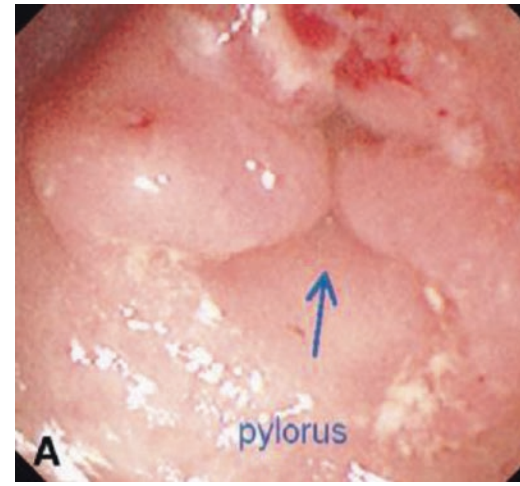

Fig. 112.22 Pre-endo-pyloromyotomy in pyloric stenosis (Permission from Dr E. Iguardo-Secchia)

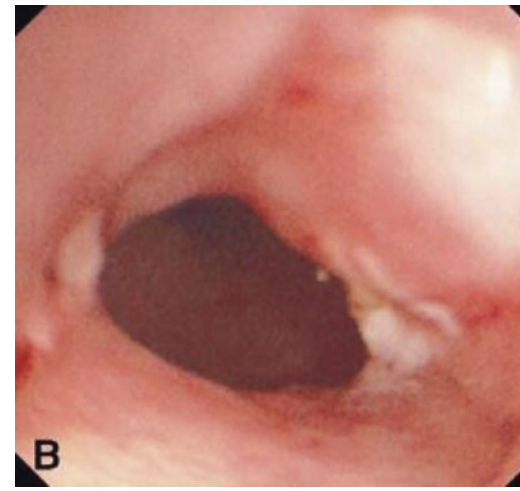

Fig. 112.23 Post-endo-pyloromyotomy in pyloric stenosis (Permission from Dr E. Iguardo-Secchia)

Percutaneous Endoscopic Gastrostomy and Gastrojejunostomy

Percutaneous endoscopic gastrostomy tubes are very commonly used since their first development by Ponsky and Gauderer 25 years ago [29]. These were devised to provide hydration and nourishment to the neurologically impaired children unable to swallow. PEG, in particular, was developed to avoid complicated surgery.

PEG tubes may be inserted using a "pull" or a "push" technique. The "pull" technique was pioneered by Ponsky and colleagues [30]. This involves performing a gastroscopy, identifying the anterior stomach wall making sure that there is no organ (particularly the spleen) that is between the wall and the skin. An angiocath is used to puncture the abdominal wall through a small incision, with insertion of a soft guidewire through this. The guidewire is pulled out of the mouth and a feeding tube attached to it and pulled through the mouth out of the incision (Figs. 112.24, 112.25, 112.26, 112.27, 112.28, 112.29, 112.30, and 112.31).

In comparison the "push" technique involves a gastroscopy to identify the anterior abdominal wall, and the wire is placed in the stomach using the Seldinger technique. A series of dilators are then used to increase the size of the gastrostomy with a tube then pushed over the wire. This is rarely performed now in children.

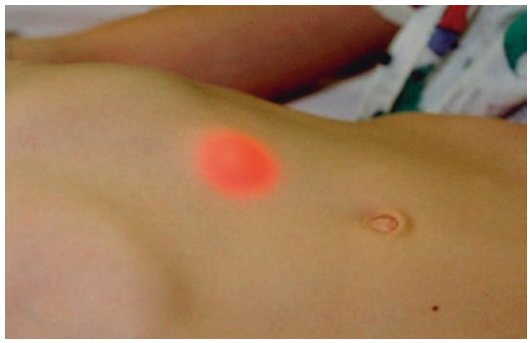

Fig. 112.24 Endoscopic transcutaneous illumination in left hypochondrium

The potential complications of gastrostomy insertion are injury to an organ such as the spleen during insertion of a gastrostomy tube, gastrocolic fistula (diarrhea may occur a short time after feeding), gastric separation, peritonitis, and gastrostomy site cellulitis (Figs. 112.32, 112.33, 112.34, 112.35, and 112.36).

Single-stage insertion of balloon gastrostomies can occur with or without laparoscopic

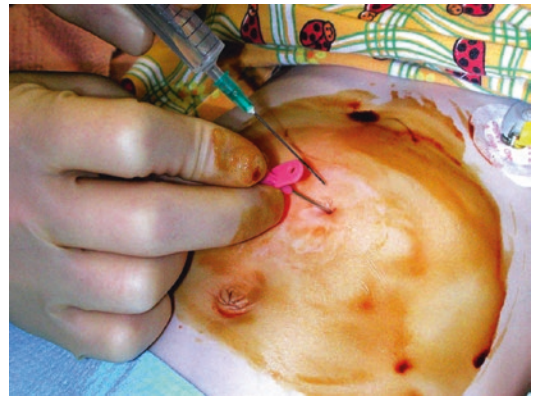

Fig. 112.25 Trochar placed through skin into gastric cavity. Note: needle with saline-filled syringe used first and inserted with suction in order to determine that the stomach is the first lumen entered, i.e., simultaneous aspiration into the stomach: the tip of needle enters the stomach and not colon. Helpful also in directing trochar insertion

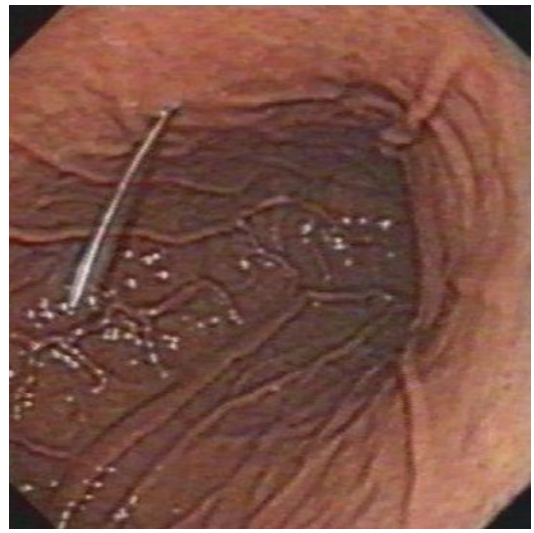

Fig. 112.26 Trochar placed into gastric cavity transcutaneously

assistance, although the blind technique using the endoscope can lead to pneumoperitoneum if not used with care. This technique has not gained wide popularity to date. Generally most operators will place a standard PEG first, allow the track to form over a period of approximately 3 months, and then perform a further endoscopy in order to change this to a correctly sized balloon gastrostomy tube, of which many exist on the market (Figs. 112.37 and 112.38).

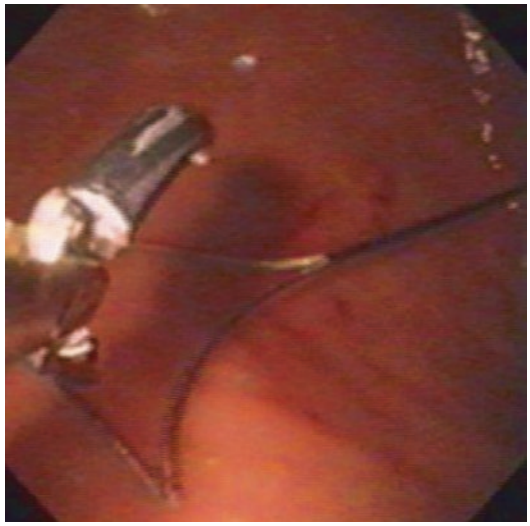

Fig. 112.27 Grasping forceps being employed to grab the wire passed through the trochar (Biopsy forceps or snare can be used)

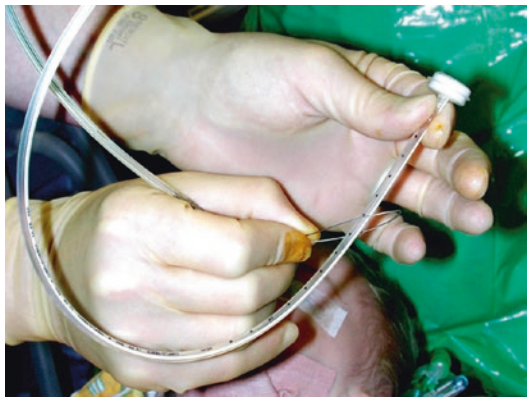

Fig. 112.28 CorFlo PEG being secured to pull-through wire which has been drawn out through the skin, stomach, and esophagus in a retrograde direction

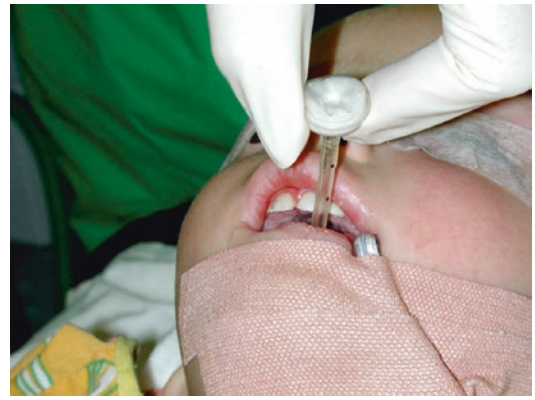

Fig. 112.29 CorFlo PEG being pulled through the mouth in an antegrade direction

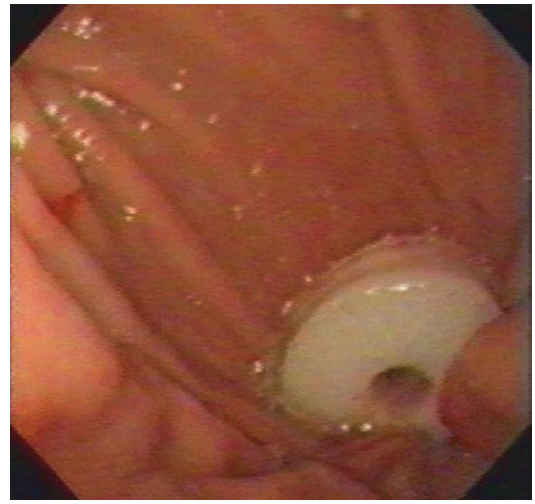

Fig. 112.30 Internal appearance of a CorFlo 12FG PEG

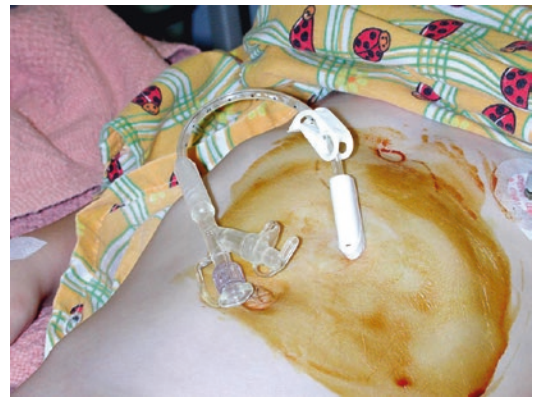

Fig. 112.31 External appearance of a 12FG CorFlo PEG

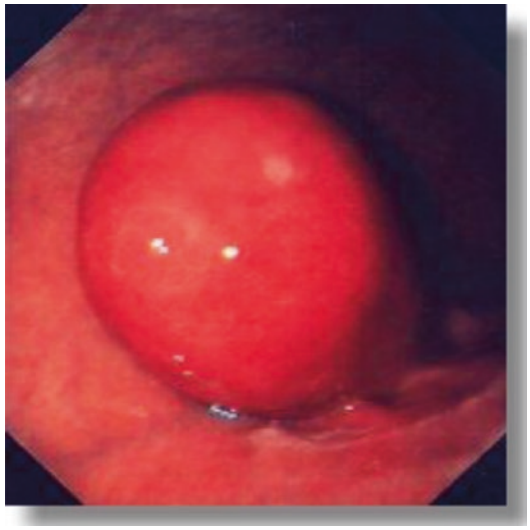

Fig. 112.32 "Buried bumper' syndrome. More common with Fresenius PEGs

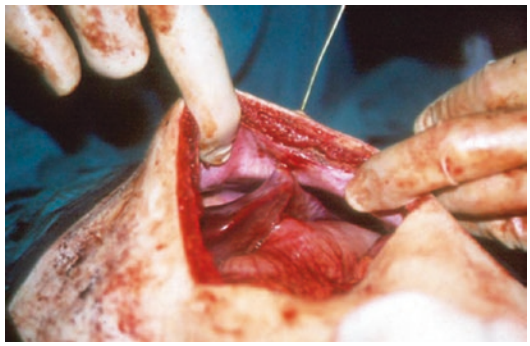

Fig. 112.33 Transhepatic PEG

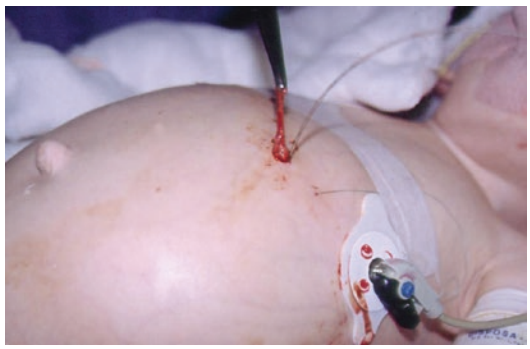

Fig. 112.34 Omentum brought out during procedure

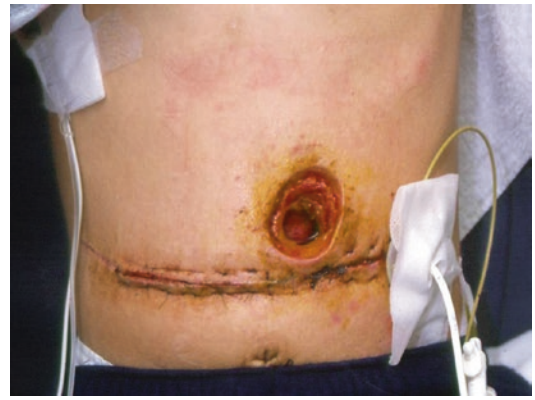

Fig. 112.35 Abdominal wall infection and dissolution

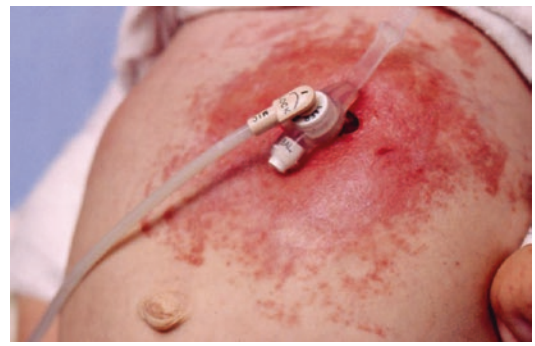

Fig. 112.36 Contact dermatitis to tape and dressing

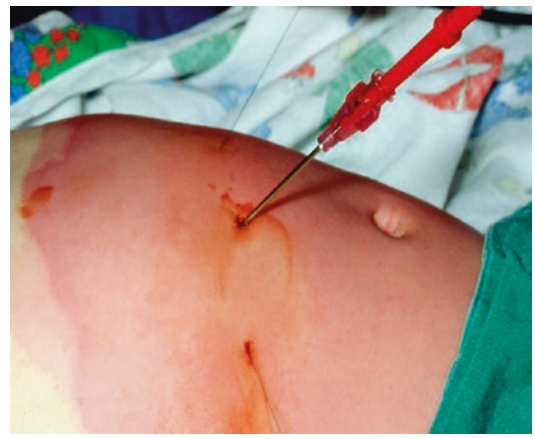

Fig. 112.37 Single-stage balloon PEG insertion. Step 1: apposition of stomach to abdominal wall with cope tags and then trochar-assisted insertion of J-wire

Using the PEG tube, it is also now possible to place a PEGJ tube. This involves placing a short PEG tube in the usual transgastric position. Through the lumen of that PEG tube, a thinner jejunostomy tube is placed. The jejunostomy tube then traverses the pylorus and extends

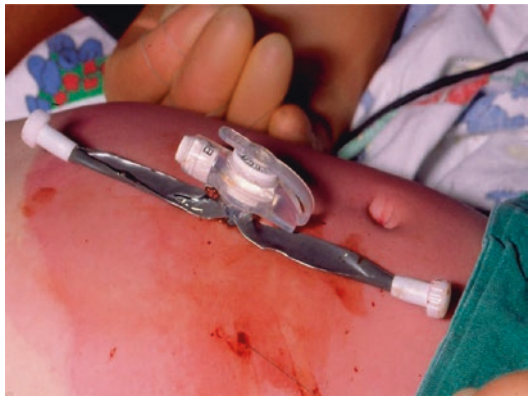

Fig. 112.38 Single-stage technique with splittable sheath placing one-step balloon gastrostomy

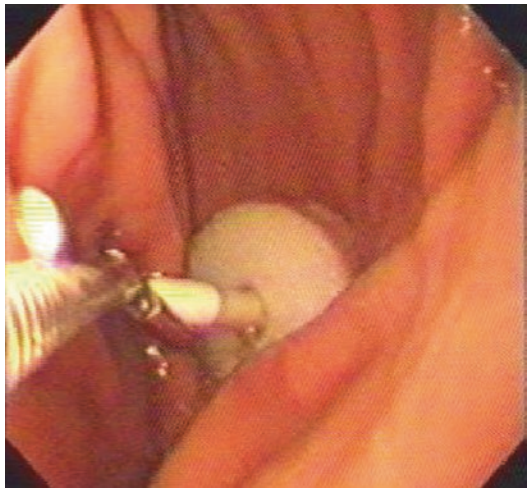

Fig. 112.39 Insertion of PEGJ lead 12FG through PEG 16FG and grabbed by grasping forceps

down beyond the ligament of Treitz. Although non-endoscopic direct placement of a PEJ tube across the abdominal wall into the proximal jejunum has also been reported, in general, jejunal tubes are fraught with problems and tend to get blocked or displaced easily. However more recently it has been possible to place a laparoscopically assisted percutaneous endoscopic PEJ with a similar technique to that employed with the PEG technique (Figs. 11 2.39, 112.40, and 112.41). Specific products and their intricacies are beyond the scope of this text, and the reader is referred to the standard pediatric endoscopic texts by Murphy et al. and Gershman et al. [3, 4].

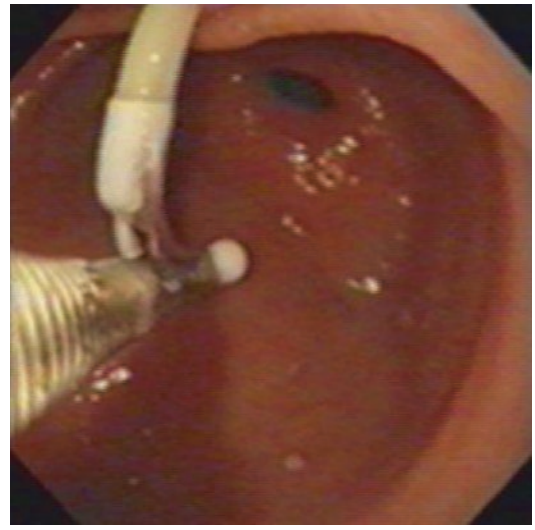

Fig. 112.40 Use of grasping forceps to place end of PEJ through pylorus

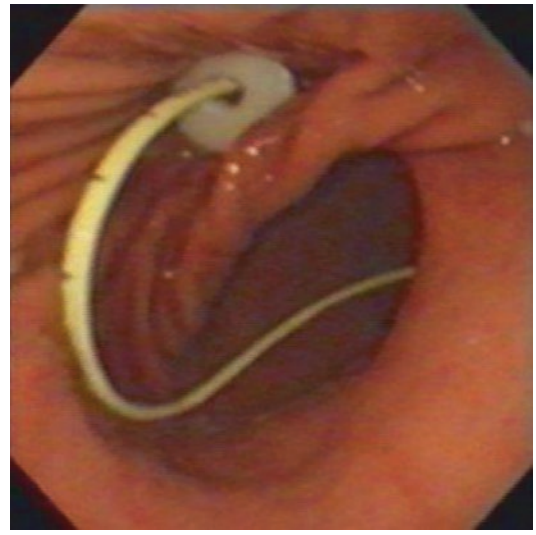

Fig. 112.41 PEJ now in situ from PEG site through pylorus

Gastric Bleeding

Although not popular for variceal treatments, due to ulcerogenic properties especially in the mid esophagus, injection of sclerosing or hemostatic agents is an option for initial treatment of gastric bleeding due to ulcers in the stomach or duodenum. It should be remembered that epinephrine injection via an endo-needle will tend to occasion

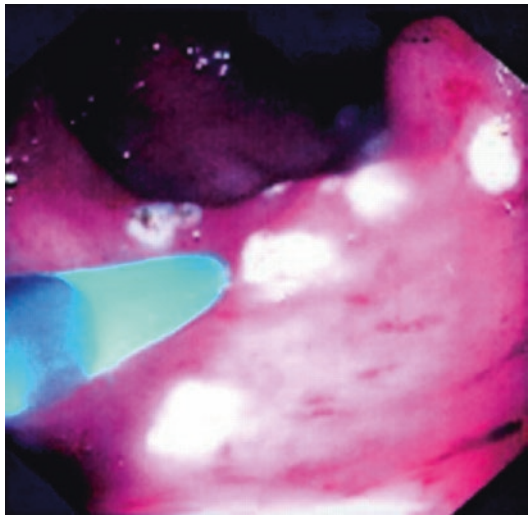

Fig. 112.42 Argon plasma probe and application in gastric bleeding

Fig. 112.43 Monopolar gold-probe electrocautery in gastric bleeding

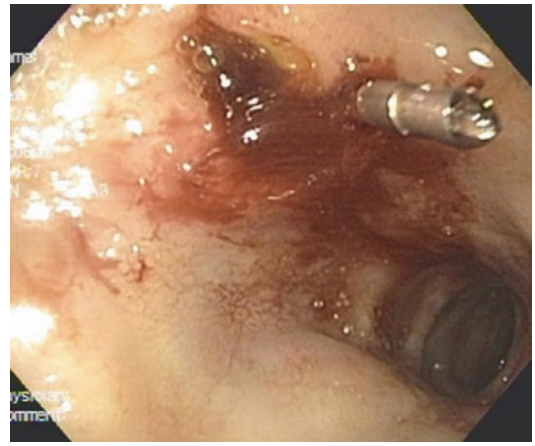

Fig. 112.44 Endoclip and application in gastric bleeding

only temporary vasospasm and bleeding cessation and will lull the operator into a false sense of security as 30 or so minutes later the bleeding may well reoccur as vasospasm resolves. Of course metal clips, referred to as endoclips delivered via the biopsy channel, can be very effective in conjunction with other techniques such as electrocautery and argon plasma coagulation in order to facilitate hemostasis. Gold-probe monopolar electrocautery (Figs. 112.42, 112.43, 112.44, 112.45, 112.46, 112.47, 112.48, 112.49, and 112.50) is also very effective for treatment of bleeding ulcers or preventing rebleeding in a patient with a non-bleeding visible vessel such as the Dieulafoy's lesion [31, 32]. Individual description of technique is beyond the scope of this chapter.

Foreign body removal is best described in the above standard endoscopic texts.

Pancreatic Cystogastrostomy

In the situation of pancreatic pseudocysts, usually the cystic mass produces a bulge into the gastric lumen, classically due to anatomical proximity, on the greater curvature. If noticeable then endo-ultrasound can be used to identify the gastric vessels and hence avoid these when subsequent incision through the gastric wall is made (Figs. 112.51, 112.52, and 112.53). The first step is to inject epinephrine into the gastric wall to prevent excessive hemorrhage following the use of the endo-knife or snare. Secondly, an incision can be made into the area where it is identified that the pseudocyst is juxtaposed to the gastric wall. This can be enlarged with a sphincterotome, and through this larger opening, pigtail cannulas can be introduced allowing drainage of the pseudocyst and subsequently prevention of closure of the fistula thus artificially created. Removal of these is not usually necessary. Symptomatic relief is usually immediate.

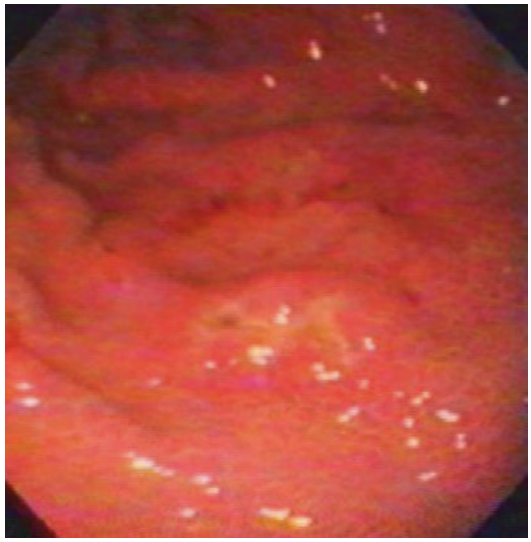

Fig. 112.45 Gastric erosion/ulcer

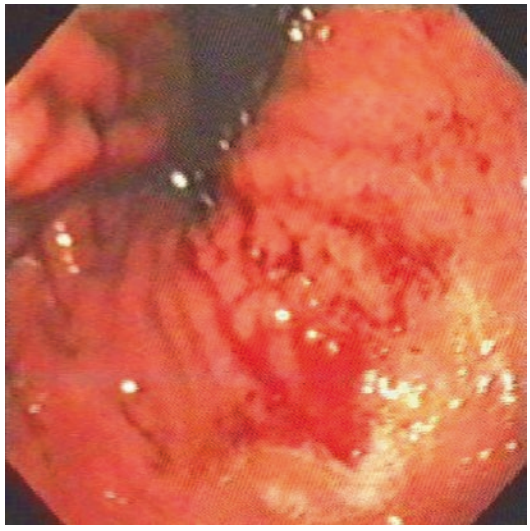

Fig. 112.46 Dieulafoy's lesion in fundus

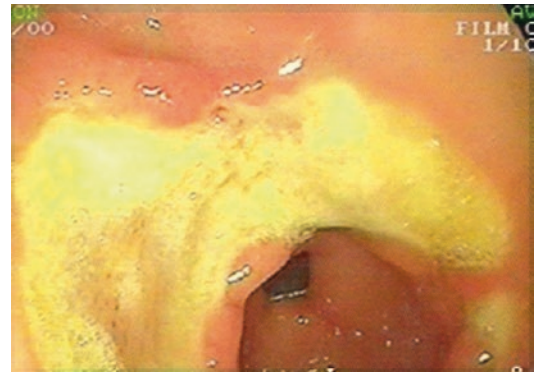

Fig. 112.47 Pre-pyloric ulcer crater with visible vessel

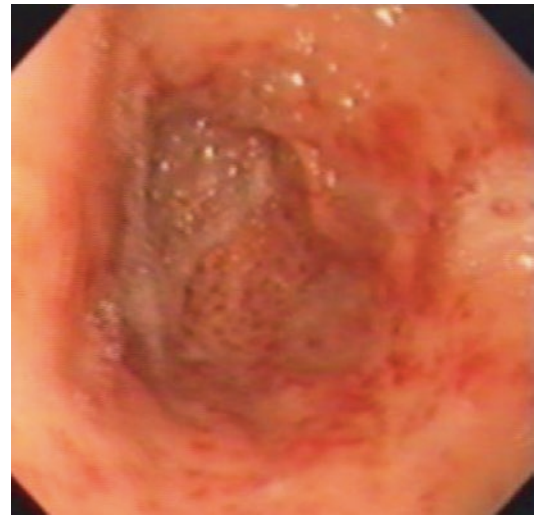

Fig. 112.48 GAVE (gastric antral vascular ectasia)

Anti-obesity Endotherapy

Balloons

The use of gastric balloons has not yet been properly explored in children or adolescents, but it has potential, especially in the medium-term accession of some weight loss, but may be not more than the initial satiety suppression that goes with gastric distension over the first few months post-insertion. Nevertheless, these devices may provide some initial inroad to weight loss, while other measures take a foothold, e.g., psychological, lifestyle management, dietary, exercise, and drug treatment (Fig. 112.54).

Endosleeve

This clever device is deployed from the duodenal cap endoscopically, and it essentially is anchored there by a self-expanding ring, which also allows subsequent endoscopic removal, and a plastic

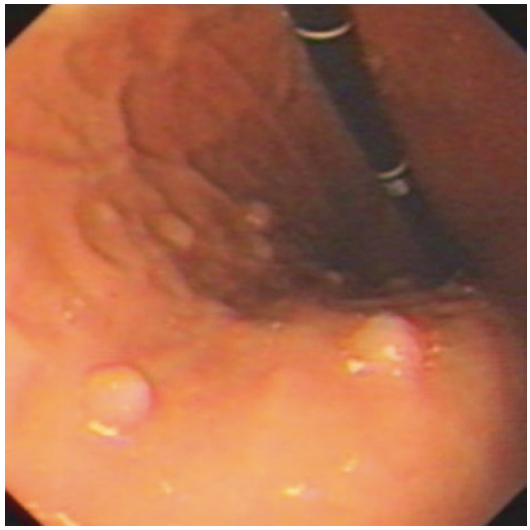

Fig. 112.49 Familial adenomatous polyposis in the stomach (FAP): incidental as do not bleed and do not undergo dysplasia

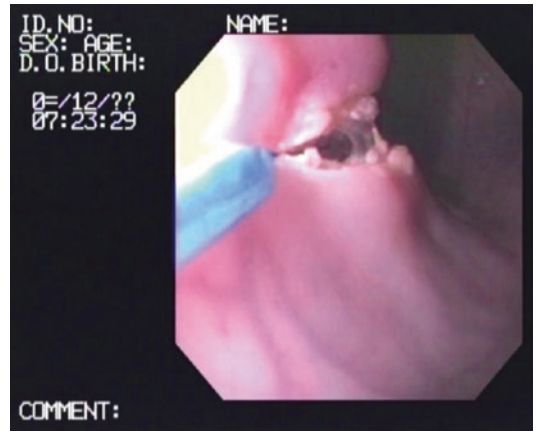

Fig. 112.51 Endo-knife incision through greater curvature of stomach into cyst, having injected adrenaline and employed endo-ultrasound to avoid gastric vessels

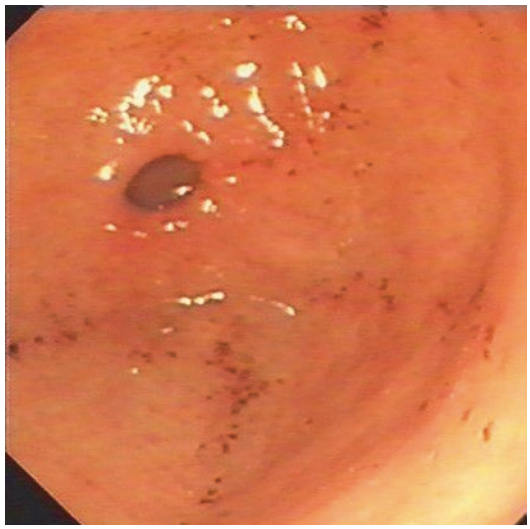

Fig. 112.50 Abrasion due to nasogastric tube tip

Fig. 112.52 Endoscopic view through gastric incision into cyst with a pigtail catheter evident

"sleeve" then is deployed distally preventing food absorption from the whole of the duodenum. It has been only used in adult studies, and its safety in children is not yet determined (Fig. 112.55).

StomaphyX

This is an endoscopic application which uses a new full-thickness plication technique by endoscopy, also used for creating a fundoplication endoscopically (EsophyX) at the GE junction, and pleats the stomach decreasing its

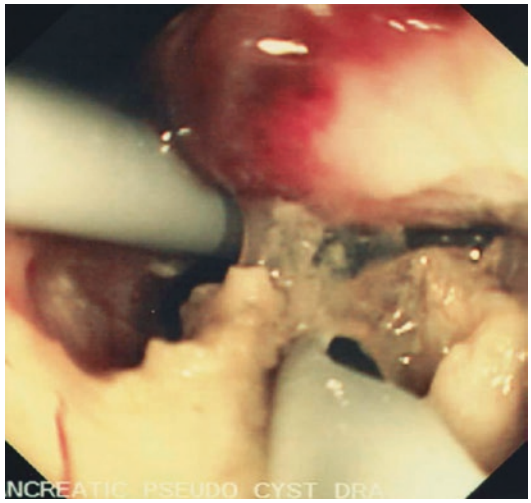

Fig. 112.53 Straight stents in situ into cyst from stomach

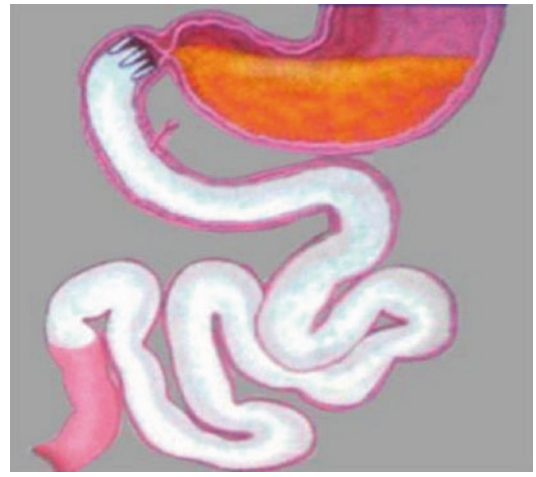

Fig. 112.55 Endosleeve preventing duodenal nutrient absorption

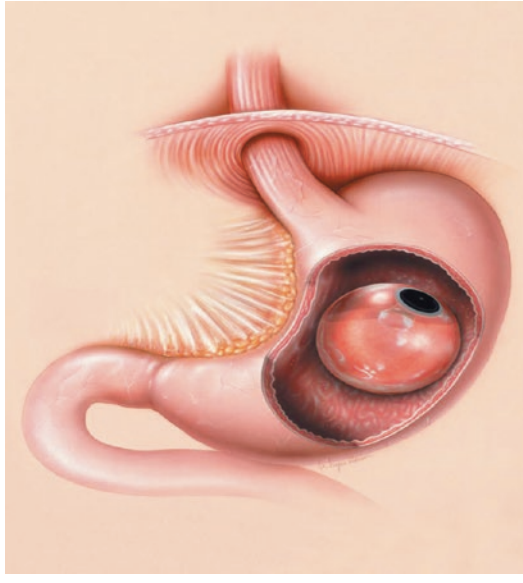

Fig. 112.54 Intragastric balloon

volume. It may be an adjunct to formal bariatric surgery, but again has not been applied in the pediatric age group (Fig. 112.56).

Endoscopic treatment of varices and NOTES are described and will not be delineated here.

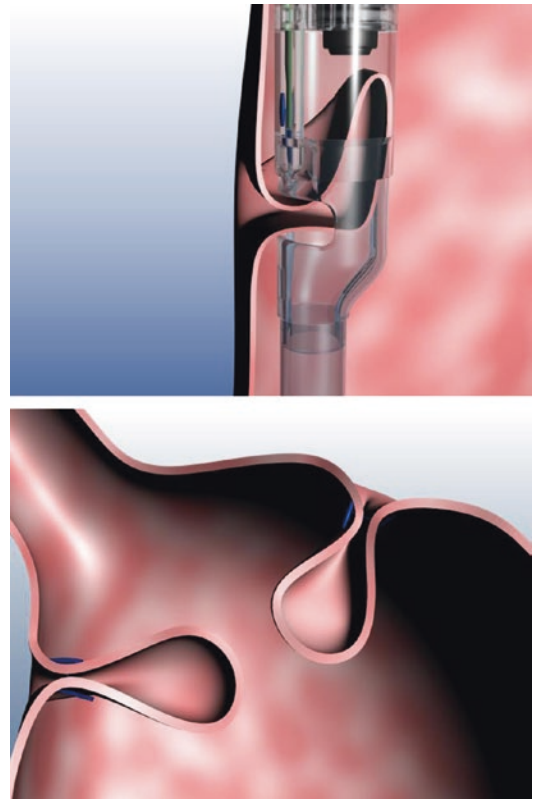

Fig. 112.56 Full-thickness transoral incisionless gastric volume diminution with StomaphyX

Summarizing, one would say that gastric endoscopy has turned the corner from diagnostic to therapeutic over the last few years and that the next decade or so may be viewed in retrospect as the time that gastroscopy came of age, mainly as a portal to natural orifice transendoluminal endoscopic surgery; however, this is still some way off.

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Radiology of the Stomach in Infants and Children

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Tara L. Holm and Charles A. Dietz Jr.

List of Abbreviations

99Tcm	Technetium 99m
cm	Centimeters
CT	Computed tomography
GE junction	Gastroesophageal junction
GIST	Gastrointestinal stromal tumor
HSP	Hypertrophic pyloric stenosis
mm	Millimeters
MRI	Magnetic resonance imaging
PET	Positron emission tomography
UGI	Fluoroscopic upper gastrointestinal series
US	Ultrasound

Imaging Evaluation of the Stomach

Imaging Overview

Radiography, fluoroscopy, ultrasound, and scintigraphy are the primary modalities for imaging the stomach in pediatric patients. Computed tomography (CT) and magnetic resonance imaging (MRI) play complimentary roles, primarily for tumor or inflammatory disease follow-up and may discover stomach pathology during the workup of abdominal pain or an unrelated condition. Imaging the stomach in infants and children requires techniques which are age- and patient condition-specific.

Ultrasound

Ultrasound imaging is the most common cross-sectional imaging modality utilized in pediatrics. Unlike CT and fluoroscopy, there is no ionizing radiation used in diagnostic ultrasound, and sedation is not required. The small size of pediatric patients allows for the use of higher-frequency ultrasound transducers, resulting in better imaging quality than is seen in adult patients. For ultrasound of the stomach and bowel, a linear high-frequency transducer is used, often 12 MHz or higher. These probes are widely available in pediatric hospitals, but may not be available in places where primarily adult patients are imaged. These transducers allow for easier discrimination between the hypoechoic muscular bowel wall and hyperechoic mucosa. Pedialyte or other clear oral liquids are often employed to distend the stomach for ultrasound evaluation. Breast milk and formula appear echogenic are not optimal for this purpose.

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Fluoroscopic Technique

Thin barium contrast is utilized in most pediatric fluoroscopic studies. Contrast may be administered via bottle, sippy cup, straw, syringe, or an enteric tube. The patient should be Nil Per Oral (=nil by mouth) (NPO) for the procedure. NPO requirements vary by institution but typically are 2 h for neonates, 4 h for infants and young children who eat solid foods, and 6 h for older children. A nasogastric tube can be used to remove liquid stomach contents in emergent cases. These examinations are usually performed with the fluoroscopic table horizontally positioned.

Older pediatric patients may be able to tolerate double-contrast examinations with thick barium contrast and effervescent crystals if fine mucosal detail is the goal of the examination. Air contrast is simulated in crying infants who swallow air. This can also be achieved in older children by puncturing the straw used to drink thin barium with a 20-gauge needle. Near-iso-osmolar nonionic water-soluble contrast is used in patients with suspected postoperative leak and may also be used in premature infants [29]. If aspirated, near-iso-osmolar nonionic water-soluble contrast is less likely to cause pulmonary edema than higher-osmolality water-soluble contrast agents and can enter the intravascular space, mediastinum, pleural space, and peritoneal cavity without complication. These contrast agents are also used intravascularly for CT. Water-soluble contrast that reaches the peritoneal space is absorbed and excreted by the kidneys [29].

The volume of contrast used for UGI depends on patient age. In premature infants and term neonates, evaluation of the stomach may require as little as 5 mL of contrast. The amount of contrast required is usually less than an infant's normal feeding volume. Older children may require 6–8 oz of contrast, depending on gastric motility and body habitus.

The radiation dose for an upper GI study can approach that of an abdominal CT. Decreasing total fluoroscopy time, using low-dose pulsed fluoroscopy, and minimizing the number of fluoroscopic spot images obtained will reduce the total radiation dose to the patient. Many pediatric radiologists have replaced fluoroscopic spot images with fluoroscopic hold images to reduce radiation. These techniques are routine in pediatric imaging facilities, but may not be regularly employed at adult imaging facilities.

Nuclear Medicine

Nuclear medicine offers functional imaging of the stomach and the ability to localize ectopic gastric mucosa and hypermetabolic gastric tumors. Technetium 99m (99Tcm) is the most common radionucleotide used in scintigraphic imaging of the stomach in children. 99Tcm-sulfur colloid-labeled formula or food can be fed to a patient to evaluate gastric emptying, gastroesophageal reflux, and aspiration. 99Tcm pertechnetate can also be given intravenously to show uptake in gastric mucosa. This agent is actively secreted by gastric mucosa and may help localize enteric duplications above or below the diaphragm [20]. The stomach may also show uptake of free 99Tcm pertechnetate if it is present as an unlabeled contaminate in a study which uses technetium bound to another agent. Gastrointestinal bleeding, including that caused by gastritis and enteric duplications, can be localized with a 99Tcm-red blood cell scan or 99Tcm-sulfur colloid-labeled scan [30]. 18Fluorodeoxy-glucose PET-CT demonstrates activity within hypermetabolic tissues and has become a useful tool in assessing response to treatment for gastrointestinal stromal tumors in both the adult and pediatric populations [3]. Similar to MRI studies, patients are required to remain motionless on the nuclear medicine gamma camera or PET scanner for a prolonged period of time, and sedation is often required for younger children. Nuclear medicine studies employ ionizing radiation in the form of gamma rays, X-rays, and emitted positrons (PET). The dose for each examination depends on the amount of radiopharmaceutical given as well as the biological and physical half-life of the radiopharmaceutical and varies by target organ.

Computed Tomography and Magnetic Resonance Imaging

CT and MR are often reserved for cases where ultrasound and fluoroscopy have not been diagnostic or for the follow-up of inflammatory or neoplastic disorders. CT involves a significant amount of radiation and should not be utilized in cases where ultrasound can answer the clinical question. CT scanning during multiple phases of contrast enhancement is common in adult CT imaging, but should be avoided in children due to the greater lifetime risk that radiation poses in children. Patients 8 years of age or older can typically follow breath-holding instructions for MR to decrease artifacts from respiratory motion. Younger patients often require sedation as the imaging time may approach 60 min. A skilled child-family life specialist and the use of video goggles in the MR scanner can reduce the need for general anesthesia in younger children [15]. MR enterography and CT enterography allow for better evaluation of the stomach wall than conventional CT and MRI. Enterography studies utilize a large quantity (e.g., 15 mL per kg) of oral contrast consumed at specific intervals before scanning to distend the stomach and bowel. One agent is a solution made of 0.1 % barium sulfate with sorbitol and guar gum to maintain luminal distention and viscosity (VoLumen, E-Z-EM, Lake Success, NY) [1]. The low CT density and low MR intensity of the enterography contrast allow for better visualization of enhancing mucosa than standard high-density oral contrast. Glucagon can also be given to slow peristalsis and decrease MR motion artifacts.

Congenital Abnormalities of the Stomach

Gastric Duplication

Ultrasound is the initial test of choice in the evaluation of suspected gastric duplications in children and is useful if the duplication is contiguous or discontinuous with the gastric wall. Ultrasound of a gastric duplication will show a thick-walled cystic structure with bowel wall signature. Bowel wall signature is a stratified pattern of echogenicity seen in any type of enteric duplication, with an echogenic central layer of mucosa, hypoechoic muscular wall, and echogenic external layer of serosa (Fig. 113.1) [24]. The internal contents of the cyst may be anechoic or contain echogenic debris. Further evaluation may be performed with CT or MRI if ultrasound is not diagnostic or if the lesion extends above the hemidiaphragm (Fig. 113.2). Fetal MRI is useful in the assessment of suspected gastric duplications discovered on prenatal ultrasound and may help differentiate between other types of abdominal cysts. Duplications which are within the wall of the stomach or that are large and cause obstruction or mass effect can also be identified fluoroscopically. On a fluoroscopic upper gastrointestinal series (UGI), this type of duplication will show extrinsic compression of the stomach with a smooth indentation at the site of the duplication, most commonly along the greater curvature [29]. If the lesion connects directly with the lumen of the stomach, the lesion itself may begin to fill with contrast, similar to a gastric diverticula. Approximately 50 % of gastrointestinal duplications found anywhere in the body contain gastric mucosa [28] and will show scintigraphic uptake of Technetium 99m, the same agent used in Meckel scans [20]. Lesions responsible for gastrointestinal bleeding may also be localized on tagged red blood cell scintigraphy.

Microgastria

Microgastria represents a congenitally small stomach which failed to undergo normal differential growth of the greater and lesser curves of the stomach and subsequent 90° clockwise rotation [22, 29]. Consequently, this appears as a small midline vertically oriented stomach with a distended esophagus and GE reflux on UGI [16, 29]. This may be seen in association with malrotation, heterotaxy syndromes (asplenia), or limb reduction defects [17].

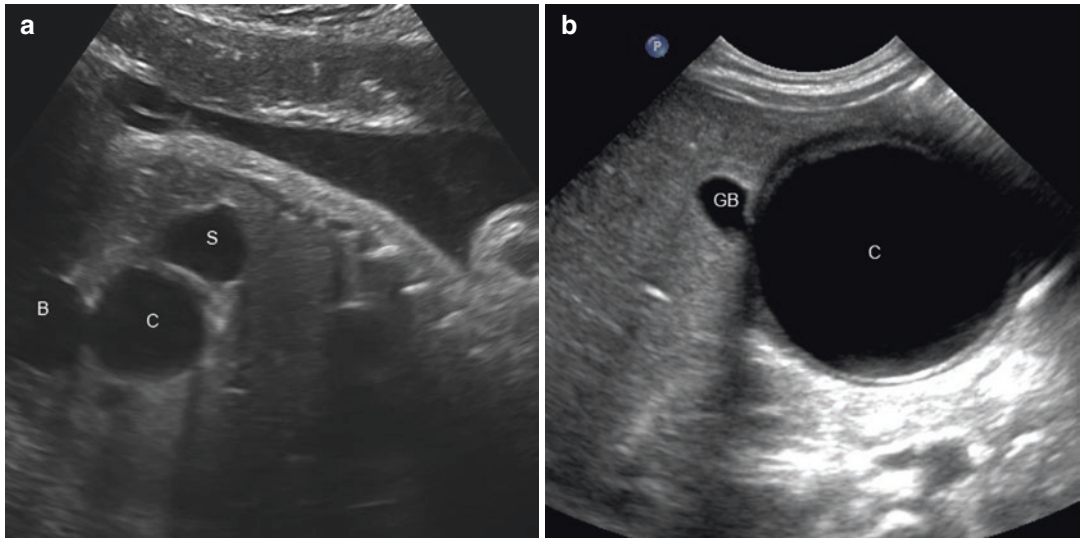

Fig. 113.1 Gastric duplication cyst. (**a**) Prenatal ultrasound image demonstrates a thick-walled cyst (*C*) positioned between the stomach (*S*) and bladder (*B*). (**b**) Postnatal ultrasound demonstrates a thick-walled cyst in the expected location of the pylorus posterior to the gall bladder (*GB*). The cyst wall consists of hyperechoic inner layer of mucosa, surrounded by hypoechoic muscle and echogenic outer layer of serosa, a pattern referred to as "bowel wall signature"

Antropyloric Web

Antropyloric web is thought to represent the consequence of a vascular accident during development and may be seen with ultrasound, UGI, and prenatal imaging [8, 29]. The web may involve the antrum or prepyloric region, and may be thick and persistent or thin and perforate spontaneously. The web creates a pseudo-double-bubble appearance with dilatation of the stomach; the body is separate from a dilated antral region and decompressed duodenal bulb. Decompression of the duodenal bulb differentiates this from the "double bubble" of duodenal atresia. The web is echogenic on ultrasound and produces "knife-like" filling defects on upper GI [8].

Ectopic Pancreatic Tissue

Ectopic pancreatic tissue has a characteristic appearance and can been seen on fluoroscopic imaging as a small round intraluminal filling defect with central umbilication often in the antral region [29]. Given the small size of this lesion, compression images of the stomach or double-contrast UGI may be required. Rarely, ectopic pancreatic tissue can be found in gastric duplications [5].

Developmental, Acquired, and Iatrogenic Conditions

Gastroesophageal Reflux

Gastroesophageal reflux (GER) is commonly present on UGI in early infancy and is considered normal when patients are growing appropriately and are not overtly symptomatic [29]. Fluoroscopically depicted GER does not equate to gastroesophageal reflux disease [6].

Upper GI fluoroscopic studies performed in children with GER are primarily performed to exclude structural reasons for emesis or feeding difficulties and can assess esophageal motility, as well as gastric emptying. Complications of GER which can be identified by UGI include esophageal dysmotility, esophagitis, and mid to distal esophageal stricture [19].

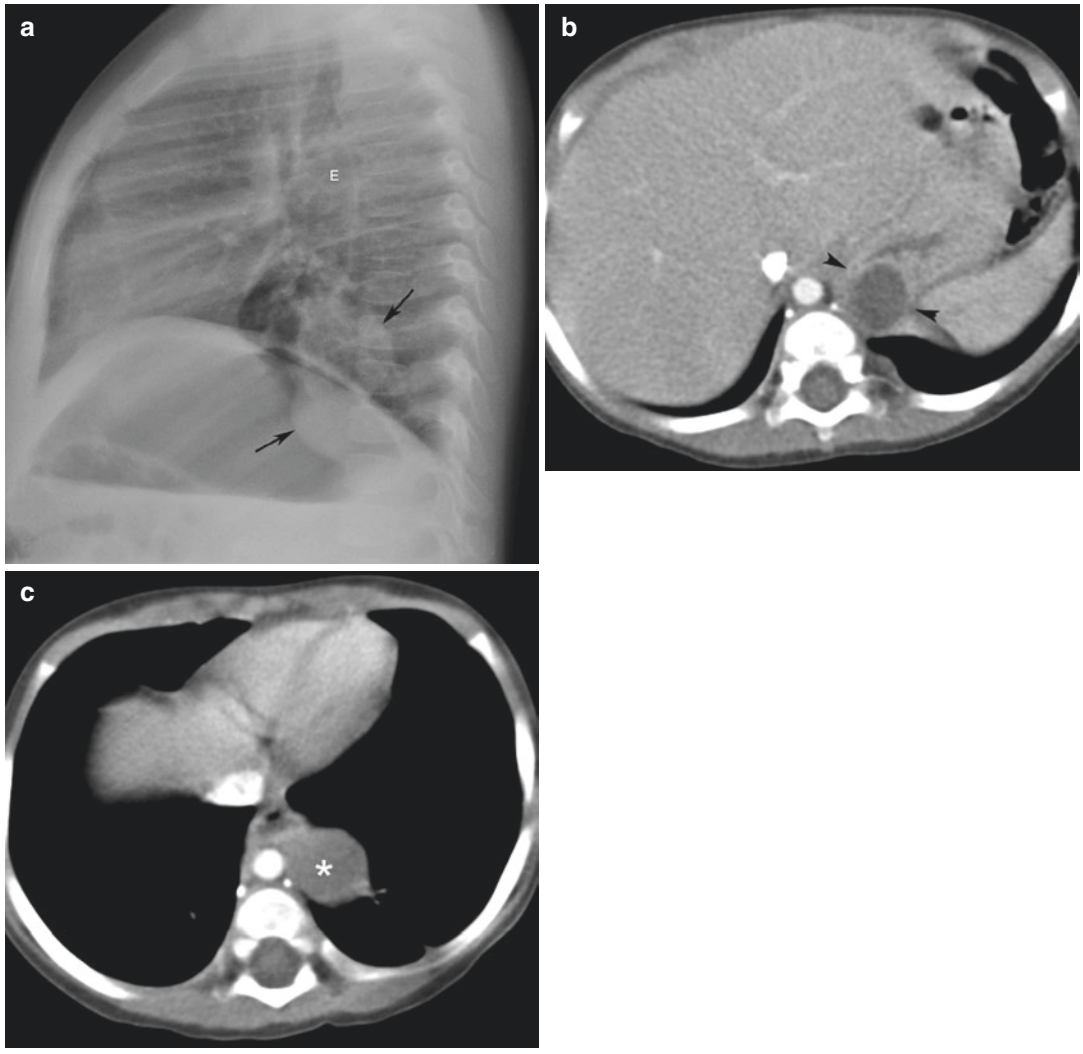

Fig. 113.2 Concurrent gastric and esophageal duplication cysts. (**a**) The lateral chest radiograph depicts a dumbbell-shaped density centered on the hemidiaphragm (*arrows*) with associated gas distention of the entire esophagus (*E*) secondary to mass effect. (**b**) Axial CT image at the level of the subdiaphragmatic portion of the duplication shows the stomach wall extending out along the medial and lateral margins of the cyst (*arrow heads*). This "claw sign" indicates origin of the cyst within the gastric wall. (**c**) Fluid density mass in the left chest (*) is the concurrent esophageal duplication

Intermittent fluoroscopy for 5 min with documentation of the frequency and level of reflux has been described as a method for quantifying GER [29]. However, this increases fluoroscopy time and ionizing radiation dose to the patient unnecessarily and should be avoided. US can be used to documenting episodes of GER, but is not widely available in the United States. Scintigraphy provides quantification of postprandial GER while also quantifying gastric emptying time, but provides little anatomic information.

Gastric Outlet Obstruction

Hypertrophic pyloric stenosis (HPS) is the most common cause of gastric outlet obstruction in early infancy [29]. Ultrasound is the initial

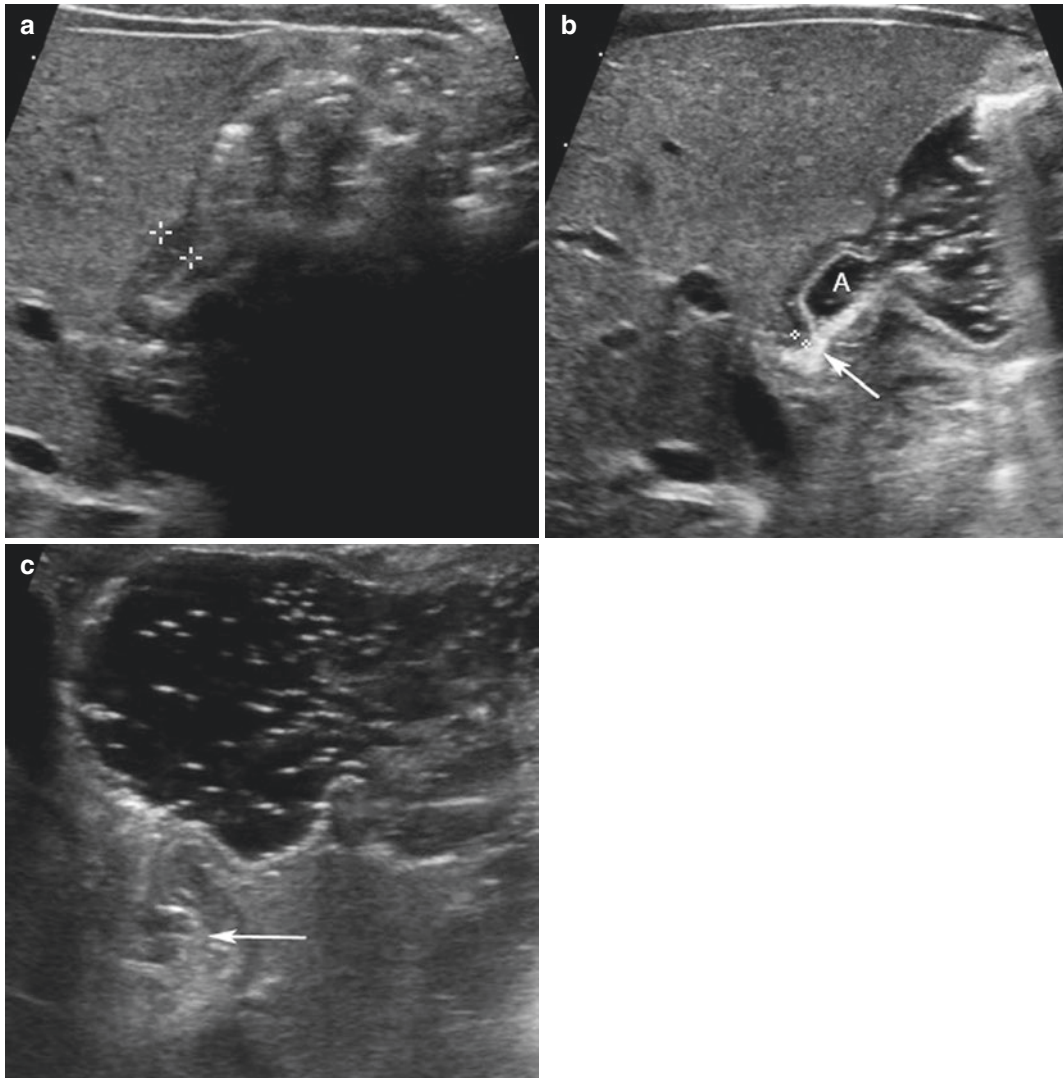

Fig. 113.3 Pylorospasm, normal pylorus, and overdistended stomach in the same patient. (**a**) Antropylorospasm is present; antropyloric wall measured 3.7 mm. (**b**) After feeding there is distention of the antrum (*A*) and a normal pyloric thickness of 1.5 mm. Liquid is passing through the pylorus (*arrow*). (**c**) Overfeeding with clear liquids pushes the pylorus posterior and difficult to assess (*arrow*)

imaging test of choice in infants between 1 week and 3 months of age with gastric outlet obstruction symptoms and nonbilious emesis.

Successful ultrasound imaging of HPS is operator dependent and is difficult if the patient is inconsolable. Feeding the patient a small quantity of clear fluids while in the right lateral decubitus position will distend the stomach and promote gastric emptying. This differentiates the pylorus from the often collapsed or contracted antropyloric region. Antropylorospasm (Fig. 113.3) is a common source of false-positive ultrasound studies for HPS [9]. Overdistention of the stomach leads to posterior displacement of the pylorus, which makes imaging more difficult. A high-frequency linear transducer is placed in oblique-transverse orientation on the right upper quadrant, and the liver is utilized as an imaging window. This will produce a longitudinal image of the pylorus posterior to the gallbladder (Fig. 113.4). Do not accept any images of the "pylorus" that include the heart. Inexperienced ultrasound technologists

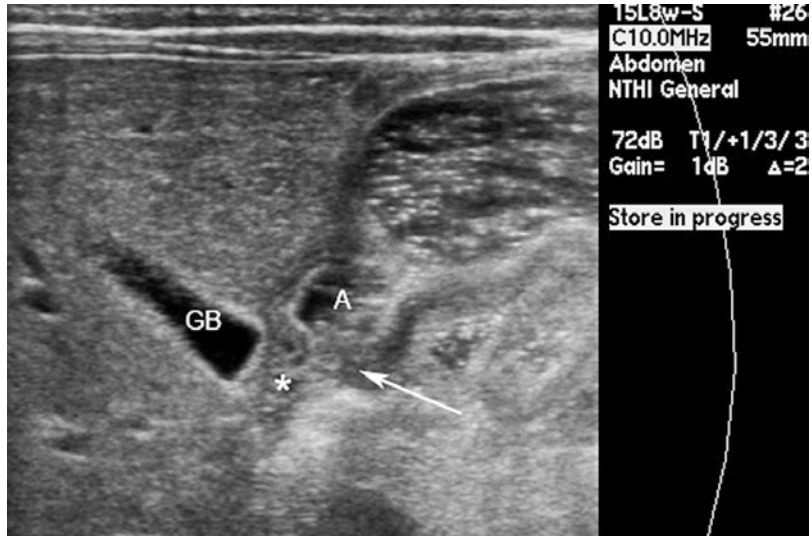

Fig. 113.4 Normal pylorus. The pylorus (*arrow*) is directly posterior and medial to the gallbladder (*GB*) The duodenal bulb is partly distended with fluid and is triangular in shape (*). Fluid distends the gastric antrum (*A*). Scanning was performed at 10 MHz

may mistake the gastroesophageal junction for the pylorus (Fig. 113.5). Pyloric muscular wall thickness can be measured in longitudinal and transverse dimensions. Measurement of a single wall of the pylorus is considered pathologic if greater than 3 mm [24]. The distal end of the pylorus is demarcated by the triangular duodenal bulb which may be filled with either fluid or echogenic gas (Fig. 113.6). Hypertrophic pyloric stenosis should appear mass-like. If no clear shouldering is seen on the antral side of the pylorus, the structure being measured may represent the collapsed gastric antrum.

The length of the pyloric channel is considered pathologic if it measures greater than 16 mm [24]. However, there is overlap between the pyloric channel length in HPS and in normal patients [29]. Haider et al. have found a direct correlation between pyloric length and birth weight in cases of HPS in small and premature infants [14]. Passage of gastric contents through a mass-like pylorus does not exclude HPS. HPS can develop quickly over the course of days, and repeat US imaging should be considered in any patient with persistent symptoms. Keckler et al. showed the pylorus can increase in thickness by up to 0.5 mm per day in HPS [18]. US imaging after pyloromyotomy demonstrates increased thickening of the pylorus in the immediate postoperative period with return to normal thickness at around the fifth postoperative month [31, 32].

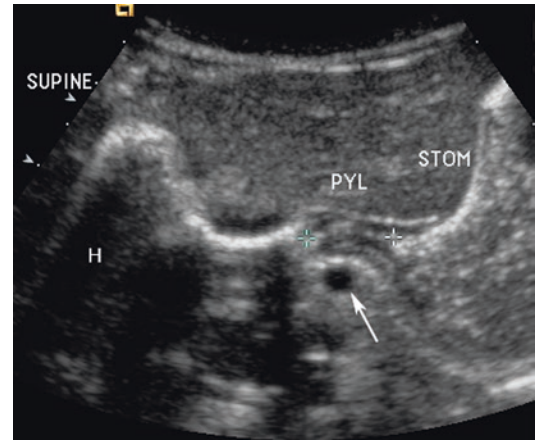

Fig. 113.5 Gastroesophageal junction is mistaken for the pylorus. The GE junction is measured and mislabeled "PYL." The descending thoracic aorta (*arrow*) is directly posterior to the GE junction. The heart is included in the image (*H*). Gallbladder is not included in the image

Documentation of the relationship between the superior mesenteric artery and superior mesenteric vein may be included in ultrasound assessment for HPS. However, a normal relationship between these vessels does not exclude malrotation. An upper GI evaluation is often performed if the pylorus is normal and the clinical picture is concerning for malrotation. This has led some to suggest that an upper GI is a more cost-effective way to evaluate HPS. However, UGI does not give pyloric wall thickness

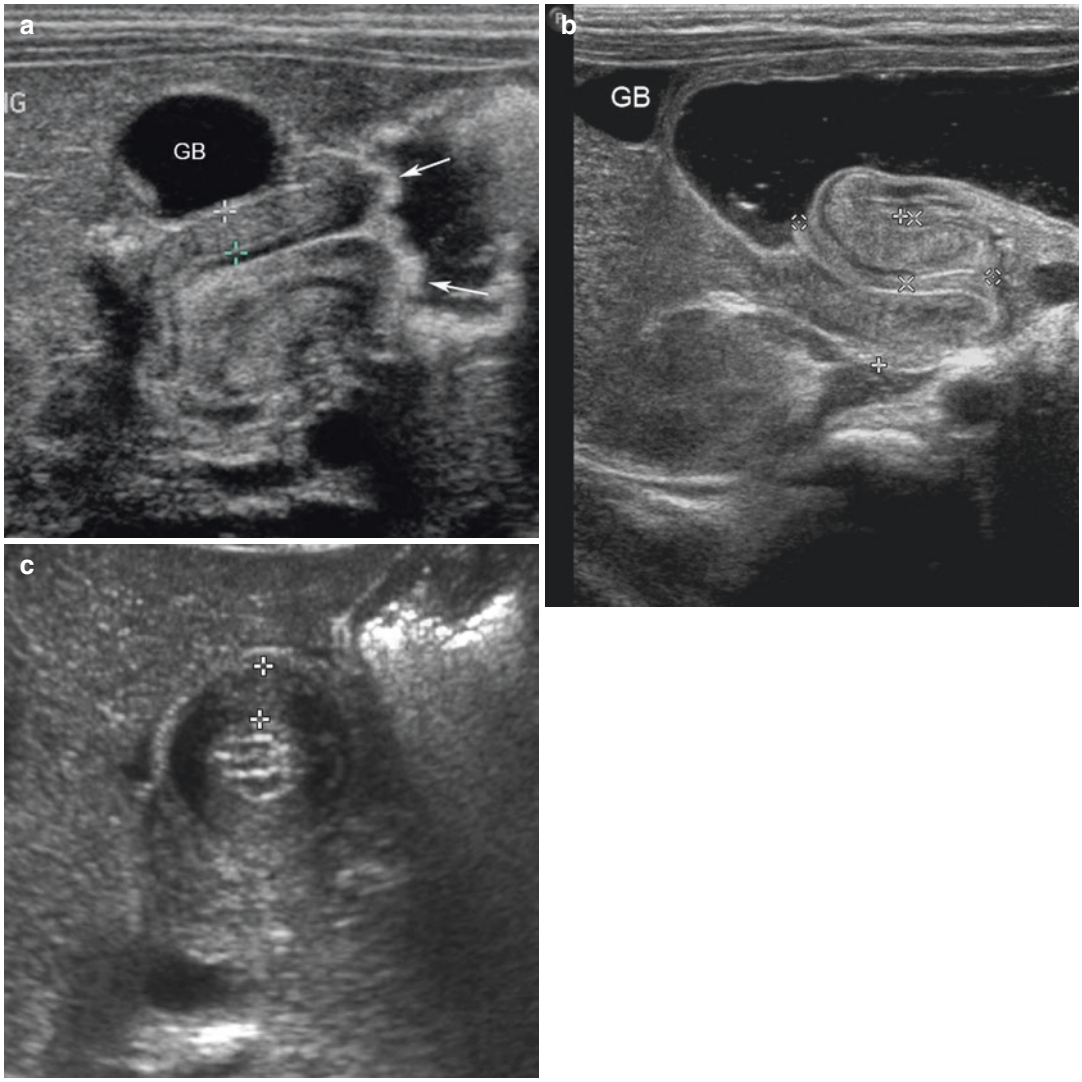

Fig. 113.6 Three patients with hypertrophic pyloric stenosis. (**a**) Pylorus is demonstrated just deep to the gallbladder (*GB*). Pyloric muscular wall thickness is 3 mm, pyloric channel is elongated, and the pylorus is mass-like with shouldering of the pylorus into the gastric antrum (*arrows*). (**b**) Similar finding is seen in a more advanced case of HPS where the pylorus is displaced posteriorly by stomach distention. Pyloric wall measures 5 mm and appears mass-like. (**c**) Transverse image of the pylorus in HPS. Measurement in the transverse plane may exaggerate pyloric thickness if the image is taken off axis

measurements and involves radiation. The fluoroscopic findings for HPS include the caterpillar sign (which represents hyperperistalsis and can also be seen by plain radiography (Fig. 113.7)), shouldering of the hypertrophied pyloric muscle, elongated narrow pyloric channel (Fig. 113.8), and significantly delayed gastric emptying [24]. UGI is also used for the assessment of persistent gastric outlet obstruction postpyloromyotomy (Fig. 113.9). Benign gastric pneumatosis may also be seen on plain radiography in HPS [4, 29].

Congenital and acquired conditions that cause gastric outlet obstruction in infants and children include antropyloric web, gastric duplications, mucosal hypertrophy in long-term prostaglandin therapy (Fig. 113.10), gastric ulcer disease, and, rarely, ectopic pancreatic tissue (Fig. 113.11) [13, 22, 27]. In obstruction due to prostaglandin therapy,

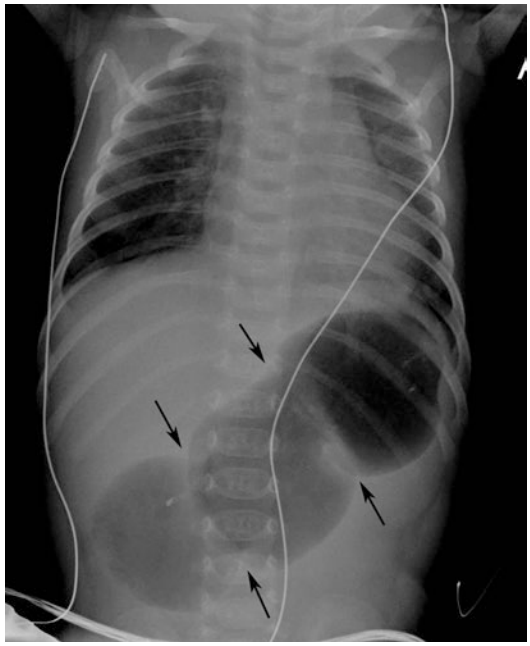

Fig. 113.7 Caterpillar sign of hypertrophic pyloric stenosis. The stomach is massively distended extending into the right lower quadrant with little distal gas. There are two indentations representing hyperperistaltic waves along the gastric contour (*arrows*)

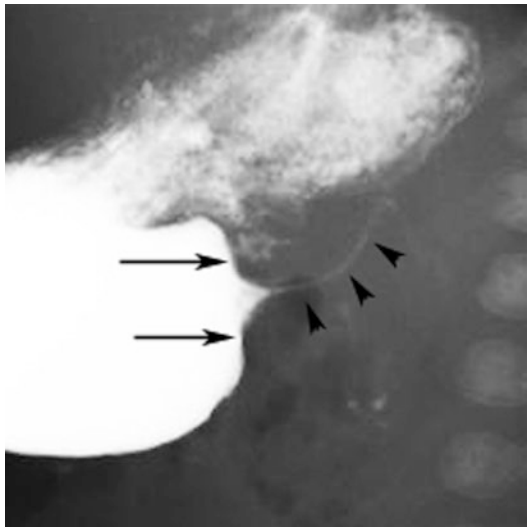

Fig. 113.8 Upper GI findings of HPS. The mass-like pylorus indents the gastric antrum; shouldering (*arrow*) the pyloric channel is elongated and narrow (*arrow heads*), and there is delayed gastric emptying (Courtesy of Dr. Steven Kraus, Cincinnati Children's Hospital and Medical Center, Cincinnati, OH)

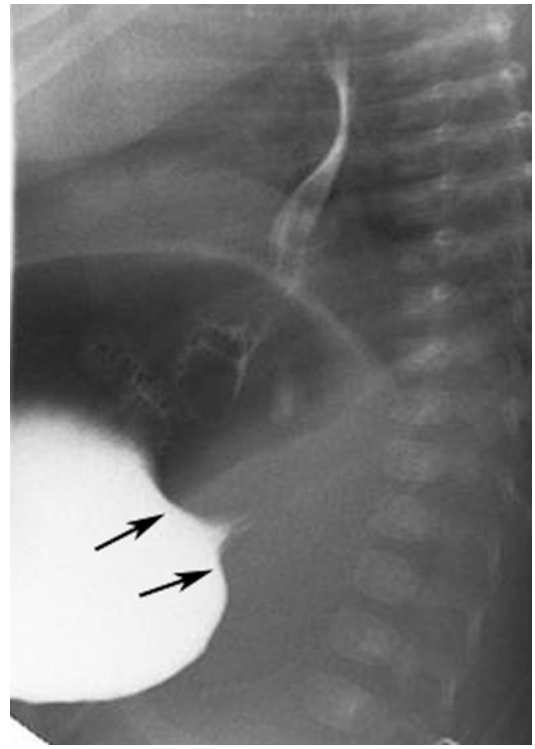

Fig. 113.9 Obstruction postpyloromyotomy. The stomach is massively distended. There is shouldering from the edematous pylorus (*arrows*) and gastric outlet obstruction which resolved spontaneously in this case

the pyloric channel is elongated, but the muscular wall thickness is normal by ultrasound [21]. Antropylorospasm may lead to significant delay in gastric emptying in normal infants during an UGI [29]. Placing the patient in the right anterior oblique or prone position on the fluoroscopy table may promote gastric emptying during the examination.

Inflammatory and Neoplastic Conditions

Stomach pathology may be found in studies performed for other reasons, such as the workup of suspected appendicitis, evaluation for weight loss or malabsorption, neoplasm follow-up, and evaluation of known inflammatory bowel disease [7]. When there is incomplete stomach distention or ingested material in the stomach, on CT or MRI wall thickening cannot reliably be determined.

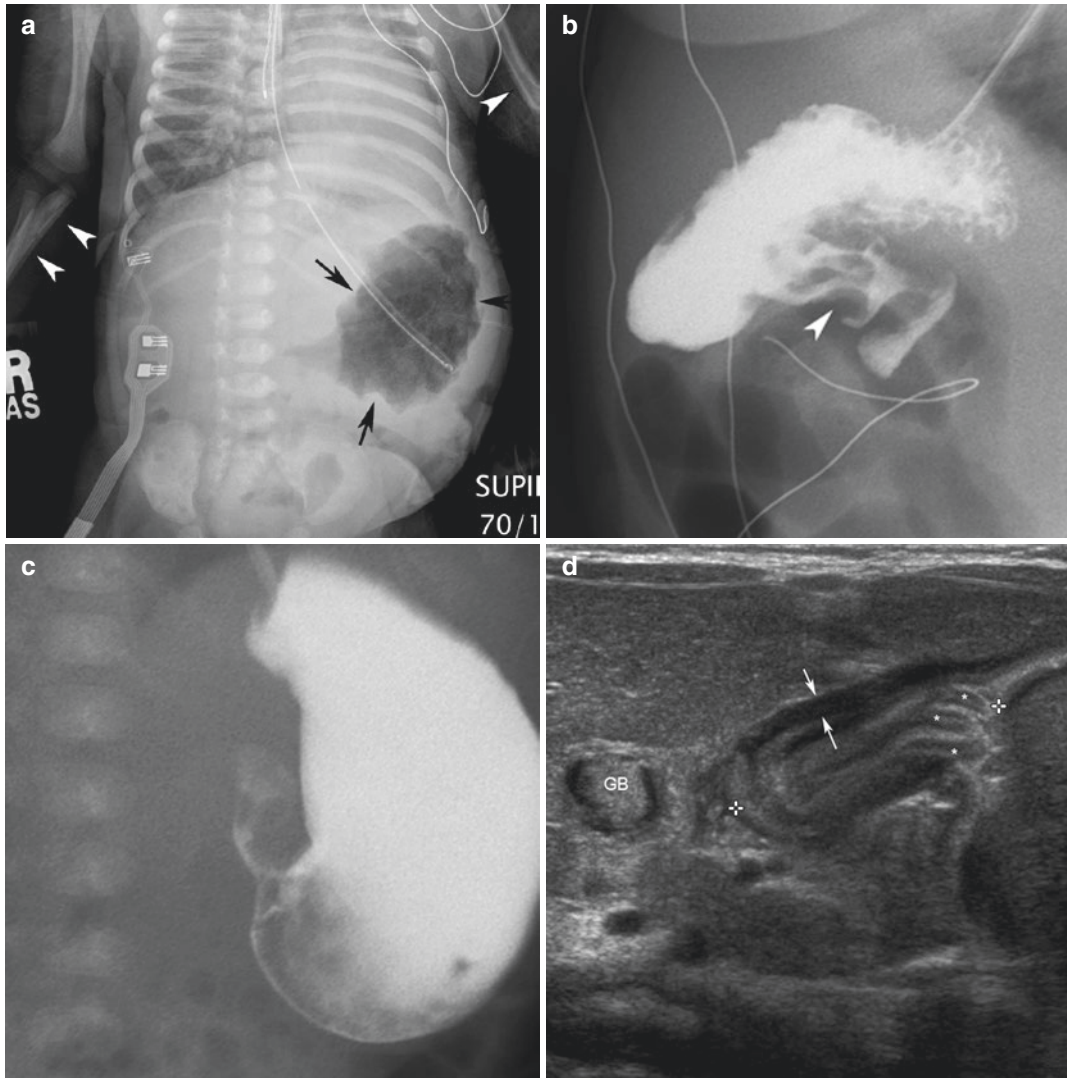

Fig. 113.10 Gastric mucosal hypertrophy in long-term prostaglandin therapy. (**a**) There is thumbprinting of the gastric mucosa (*arrows*) and diffuse long bone periostitis (*arrow heads*) in an infant with interrupted aortic arch and feeding intolerance. (**b**) UGI demonstrated markedly thickened mucosal folds in the gastric antrum (*arrow head*) and mildly delayed gastric emptying. (**c**) Gastric outlet obstruction mimics HPS in this patient with tetralogy of Fallot and pulmonary atresia. (**d**) The pyloric channel is elongated measuring (+ calipers) 25 mm, with normal muscular wall thickness of 2 mm (*arrow heads*). Several mucosal folds are present in the pyloric channel (*). Gallbladder is sludge filled (*GB*)

However, with adequate distention, wall thickening may be identified (Fig. 113.12). Crohn's disease of the stomach is uncommon, especially in children, but may result in chronic narrowing of the antropyloric region on UGI [12]. Tuberculosis of the stomach results in similar findings [23, 24]. CT and MR enterography studies have recently been utilized in the imaging of inflammatory bowel disease. Active Crohn's disease of the stomach is usually seen as wall thickening and hyperenhancement of the distal stomach. The large quantity and type of oral contrast consumed in the enterography protocols produce superior delineation of the stomach wall to that which can be seen on routine abdominal CT or MRI (Fig. 113.13). UGI may also reveal mucosal thickening in gastritis associated with *H. pylori*, chemical ingestion, eosinophilic gastritis, graft-versus-host disease,

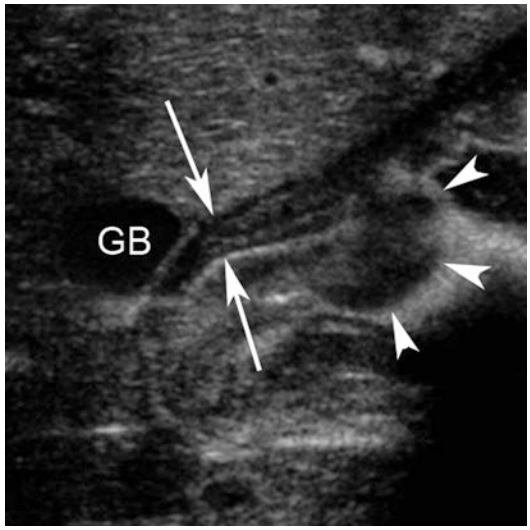

Fig. 113.11 Ectopic pancreatic tissue resulting in gastric outlet obstruction in a 2-day-old infant. Round nodule of ectopic pancreatic tissue (*arrowheads*) is present along the anterior antropyloric wall and mimics the findings of hypertrophic pyloric stenosis. However, the pyloric muscular wall is not thickened (*arrows*). Pylorus is directly adjacent to the gallbladder (*GB*)

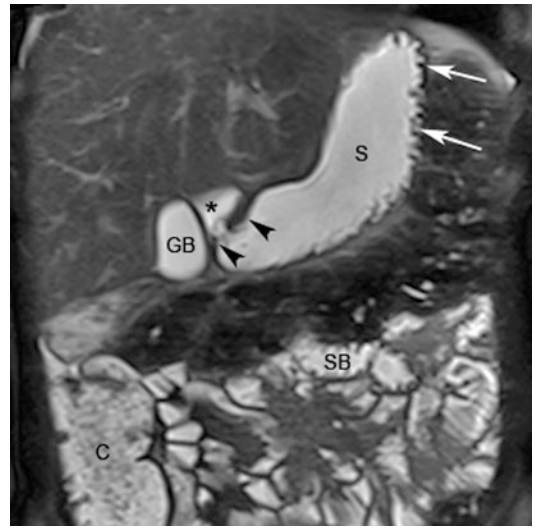

Fig. 113.13 Normal appearance of the stomach, MR enterography. The stomach (S) is well distended by biphasic oral contrast. The pylorus (*arrowheads*) and duodenal bulb (*) are directly medial to the gallbladder (*GB*). Normal rugal folds (*arrows*) are best seen in the fundus. Normal mucosal pattern is also seen in the small bowel (*SB*) and colon (*C*)

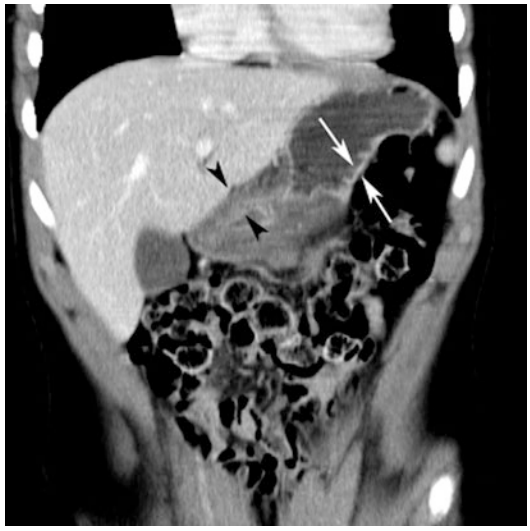

Fig. 113.12 Gastric ulcer disease. Coronal CT in an otherwise healthy 12-year-old boy with abdominal pain and nonbilious emesis demonstrates massive thickening of the stomach wall in the gastric antrum (*arrowheads*) and normal wall thickness in the fundus of the stomach (*arrows*) due to large peptic ulcers involving the antrum and pylorus

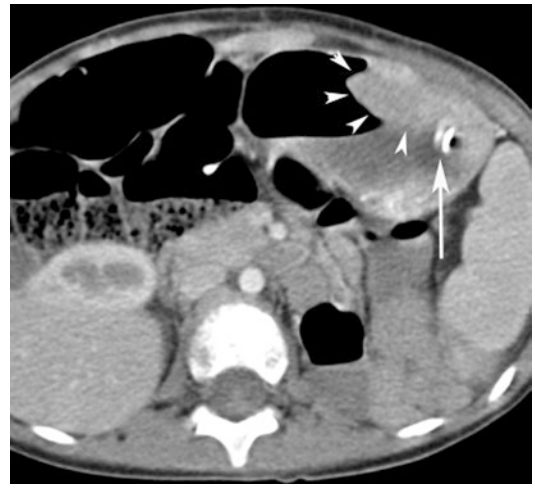

Fig. 113.14 Gastric lymphoma. CT surveillance in a transplant patient reveals a mass arising from the anterior gastric wall (*arrowheads*) directly adjacent to the patient's gastrostomy tube balloon (*arrow*). The mass is outlined partially by gas, but is also obscured by fluid within the stomach posteriorly (Courtesy of Dr. Brenda Weigel, Minneapolis, MN)

and Menetrier's disease [29]. Childhood gastric tumors are rare [3, 33] and appear as a solid mass contiguous with the stomach wall, best seen when outlined by air or contrast (Fig. 113.14). PET-CT is utilized in the evaluation of gastrointestinal stromal tumors, as described previously [3].

Postoperative Imaging Studies

Gastrostomy tube evaluation is a common pediatric fluoroscopic study. Water-soluble contrast is injected to confirm tube placement within the stomach and to outline the retention balloon. Lateral imaging tangential to the gastrostomy tube skin entry site is essential to show the retention balloon is not inflated within the abdominal wall (Fig. 113.15). Contrast passage into the duodenum and stomach is documented to exclude pyloric obstruction from the retention balloon in the antral region or pylorus (Fig. 113.16). When a gastrostomy tube is malpositioned in the peritoneal space, injected contrast flows dependently and may outline loops of the bowel.

Nissen fundoplication creates a characteristic filling defect just lateral to the gastroesophageal junction on UGI (Fig. 113.17). Contrast may also be seen within the Nissen wrap. However, this does not cause recurrent reflux in all cases [29]. Hiatal hernia or slipped Nissen is identified when the stomach extends above the level of the medial left hemidiaphragm and is best seen on oblique views during UGI. If the patient has no gastroesophageal reflux, a small amount of contrast is given from above to demonstrate the position of the GE junction and differentiate a paraesophageal hernia from a sliding hiatal hernia. The GE junction is below the hemidiaphragm in paraesophageal hernia and above the hemidiaphragm in hiatal hernia

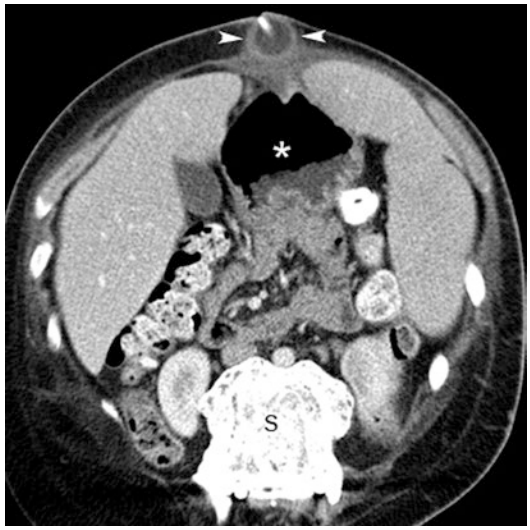

Fig. 113.15 Malpositioned gastrostomy tube. The gastrostomy tube retention balloon (*arrowheads*) is inflated within the anterior abdominal wall, displaced from the stomach antrum (*). The tube was malfunctioning, but the patient was asymptomatic due to decreased sensation from a remote spinal injury (*S*)

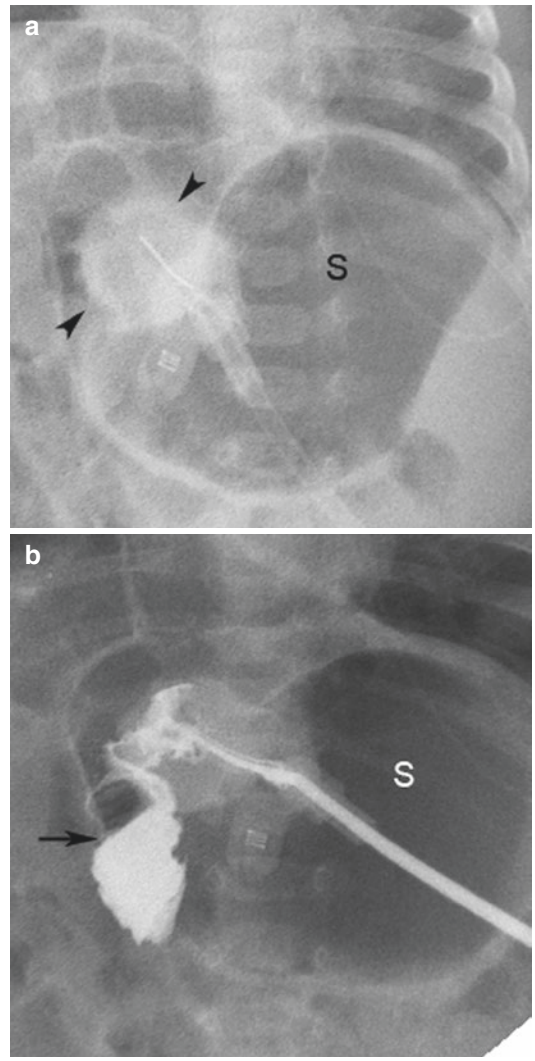

Fig. 113.16 Malpositioned gastrostomy tube. (**a**) The stomach is distended (S) and the retention balloon (*arrowheads*) is at the expected location of the pylorus. (**b**) Injected contrast passes directly into the duodenum (*arrow*) confirming that the retention balloon was inflated at or past the pylorus. (**c**) After deflation and repositioning, the retention balloon (*arrowheads*) is outlined by contrast along the greater curvature of the now decompressed stomach (*S*). Pylorus (*arrows*)

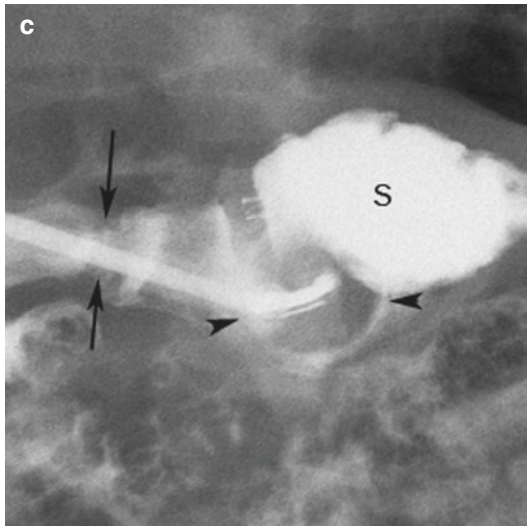

Fig. 113.16 (continued)

Fig. 113.17 Nissen fundoplication defect. Contrast has been injected through the patient's gastrostomy tube. The stomach is well filled and there is no gastroesophageal reflux. There is a small irregular filling defect at the GE junction (*arrows*) which is typical for Nissen fundoplication. The small bowel is malrotated (*arrowheads*)

[19]. If swallowed contrast fails to pass into the stomach in the supine position, it is useful to reassess after the patient has been upright.

Refluxing contrast into the distal esophagus via gastrostomy tube injection is useful in determining the length of the distal esophagus

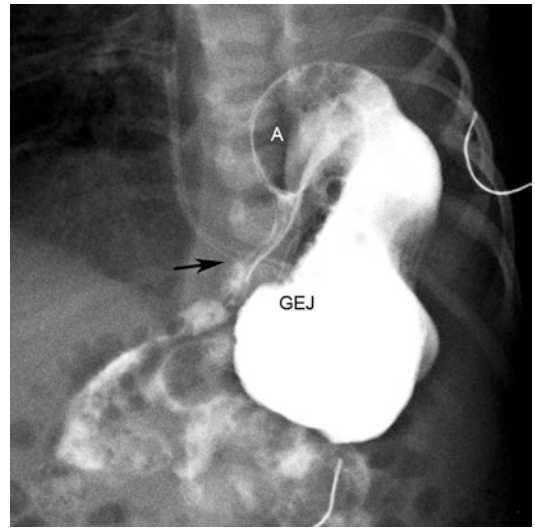

Fig. 113.18 Mesenteroaxial gastric volvulus in an asymptomatic newborn with left lung agenesis and complex spine and chest wall deformities. The stomach is displaced into the left hemithorax due to a congenital diaphragmatic hernia. The gastric antrum (*A*) is positioned superior and anterior to the gastroesophageal junction (*GEJ*). The distal esophagus and elongated antropyloric region cross overlying the spine (*arrow*)

in esophageal atresia and is also useful in finding esophageal leak postesophageal atresia repair.

Emergent Conditions

Gastric Volvulus

Another cause of nonbilious emesis is gastric volvulus. Imaging studies may show an elevated left hemidiaphragm or diaphragmatic hernia both of which are associated with poor ligamentous fixation of the stomach [11]. In acute volvulus radiographs may show a double air-fluid level [19]. On UGI or CT mesenteroaxial volvulus results in the pylorus being positioned superior and anterior to the gastroesophageal junction [19, 29] with an unusually vertical orientation of the stomach (Fig. 113.18). If there is an associated hernia, contrast may remain in the abdominal portion of the stomach due to obstruction at the site of herniation (Fig. 113.19). Organoaxial volvulus

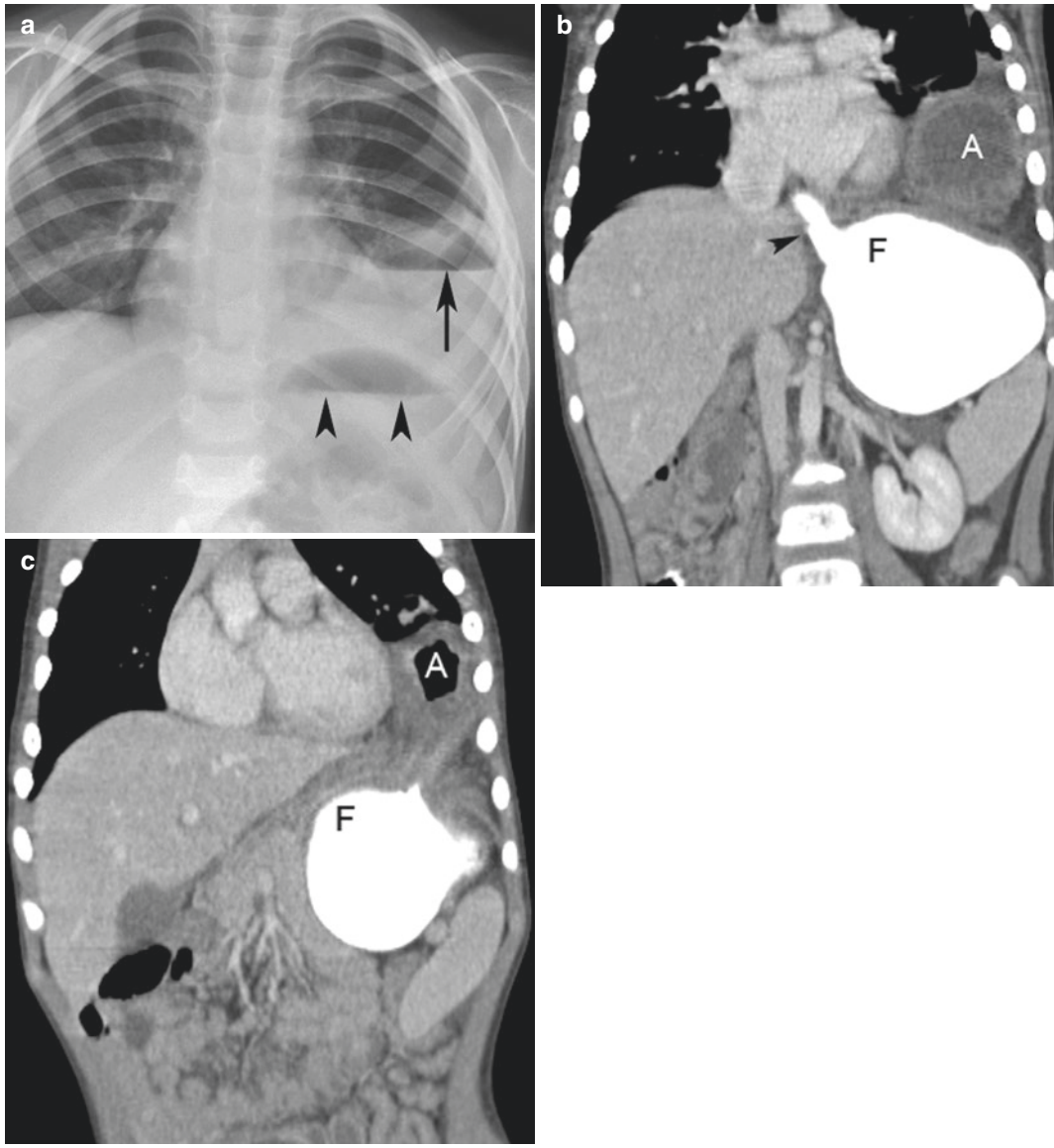

Fig. 113.19 Acute mesenteroaxial gastric volvulus. (**a**) Chest radiograph demonstrates a fluid-gas level in the left hemithorax (*arrow*) and in the expected position of the gastric fundus (*arrowheads*). (**b**, **c**) There are contrasts in the gastric fundus, (*F*) which remains in its expected location, and within the esophagus (*arrowhead*). However, there is no contrast in the stomach antrum (*A*) which has herniated into the left hemithorax (Courtesy of Dr. Eric Hoggard, Minneapolis, MN.)

results in horizontal orientation of the stomach with the greater curvature positioned superior to the gastroesophageal junction. The stomach may assume a similar position in neonates due to circulating maternal hormones and has been described as a "floppy stomach" to differentiate this from a true volvulus [26].

Gastric Perforation

A large amount of free intraperitoneal air in a neonate suggests gastric perforation. This may be seen as a contiguous diaphragm sign, Rigler's sign, outlining of the ligamentum teres by air, or triangular-shaped regions of gas or unusual

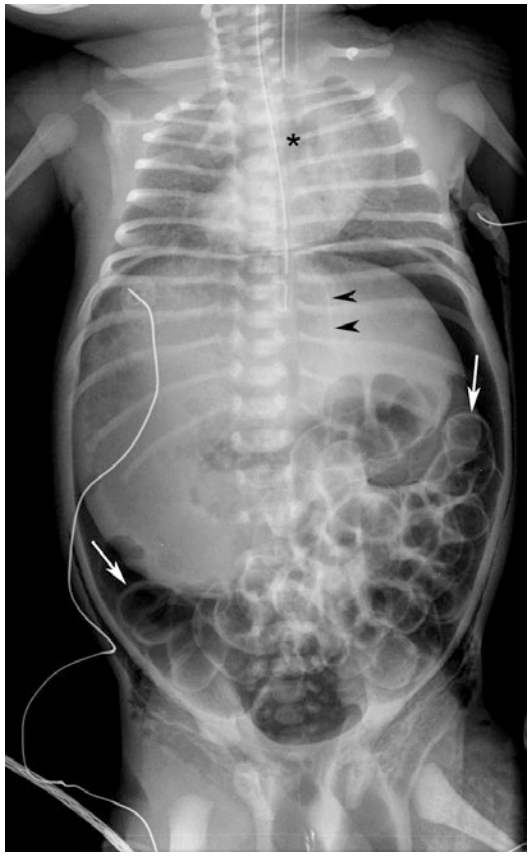

Fig. 113.20 Iatrogenic stomach perforation in a complicated neonate with situs inversus. There is massive free air in the abdomen. Air outlines the ligamentum teres, known as the "football sign" (*arrowheads*). Gas also outlines both sides of the bowel wall, known as the "Rigler's sign" (*arrows*). Gas has tracked into the chest causing pneumomediastinum (*), pelvic subcutaneous tissues, scrotum bilaterally, and the tissue planes of the left thigh

lucent area over the liver on supine images, and can be confirmed by cross-table lateral or lateral decubitus radiographs. Gastric perforation is seen spontaneously in neonates from birth trauma and can be seen in patients of any age due to iatrogenic perforation after enteric intubation or from gastric ulceration (Fig. 113.20).

Foreign Bodies

Ingested foreign bodies such as coins and coin-shaped batteries are likely to pass from the stomach if they are demonstrated below the GE

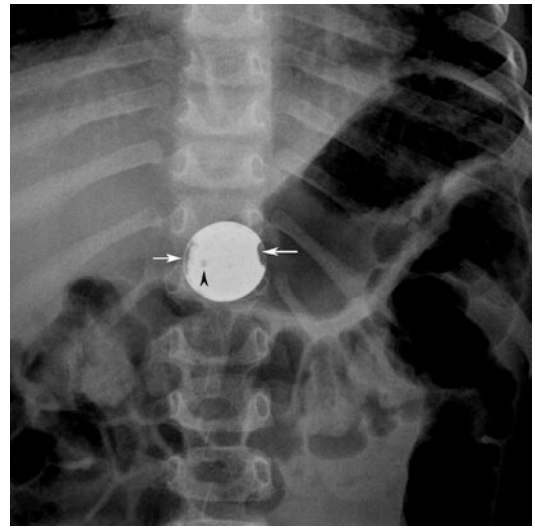

Fig. 113.21 Retained gastric penny. Round metallic foreign body projects over the gastric antrum. The object is eroded at its lateral margins (*arrows*) and centrally (*arrowhead*). Radiographically this cannot be distinguished from an eroded coin-shaped battery

junction on plain radiographs [2, 3]. However, if a penny fails to pass from the stomach, the copper coating erodes, and the underlying zinc is exposed, which may lead to gastric ulcers and anemia (Fig. 113.21). If eroded margins or holes are radiographically evident, the penny should be endoscopically removed [25]. Other radiopaque-ingested hazards include magnets (which can cause enteric perforations), bones, and lead-based objects including jewelry. Many ingested materials are radiolucent and are not detectable by plain radiographs. UGI and CT are imaging options for non-radiopaque stomach foreign bodies including thin metallic objects such as aluminum can tabs.

Hair and high-fiber vegetable matter are common ingested materials seen in childhood bezoar (Fig. 113.22) [29]. Bezoars may be seen as an intraluminal stomach mass on plain radiography, fluoroscopic studies, ultrasound, or CT. However, UGI is the initial test of choice [19]. Trichobezoar is seen as an echogenic mass on ultrasound due to gas trapped within the mass of hair. If a trichobezoar extends into the duodenum and small bowel (Rapunzel syndrome), findings of small bowel obstruction may also be present [10, 31]. Ingested

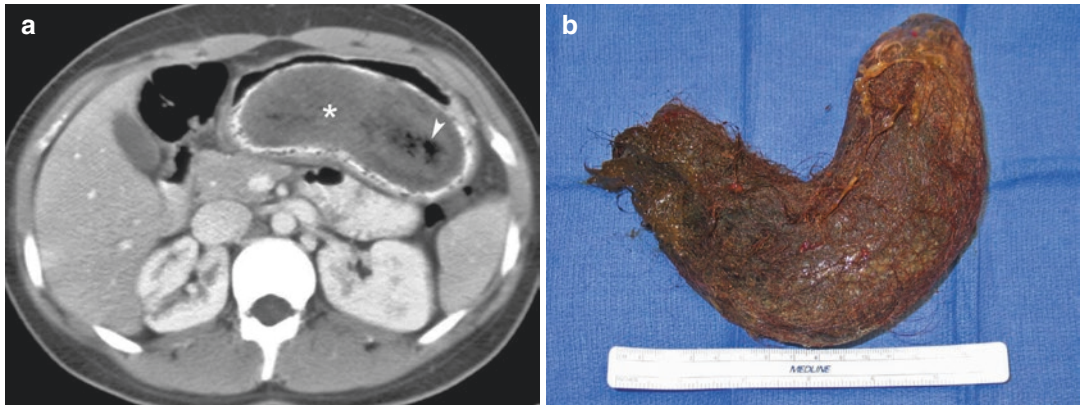

Fig. 113.22 Trichobezoar. (**a**) Axial CT demonstrates a heterogeneous mass of hair (*) and trapped air bubbles (*arrowhead*) distending the stomach, surrounded by contrast posteriorly and air anteriorly. (**b**) The trichobezoar gross specimen conforms to the shape of the stomach (Courtesy of Dr. Hank Baskin, Salt Lake City, UT)

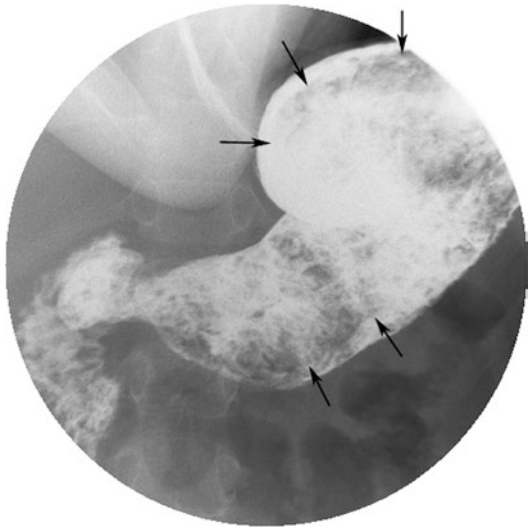

Fig. 113.23 Retained food mimicking bezoar in an autistic child. The stomach is mildly distended with a large immobile filling defect (*arrows*) composed of recently ingested French fries

food may mimic a bezoar if the patient is not appropriately NPO for a fluoroscopic study (Fig. 113.23). Delayed images of the stomach are useful in this circumstance.

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Gastric Motility and Electrogastrography (EGG)

114

Alberto Ravelli

Introduction

The physiology and pathophysiology of gastrointestinal motility in the human infant and child are only partially understood. This is largely due to the fact that invasive and unpleasant investigations are usually required to study contractile activity and transit through the gut. In fact, such invasive investigations are less acceptable and on average poorly tolerated by both infants and children, and therefore systematic studies are severely limited. The constraints imposed by such poor acceptability of extensive motility studies in childhood are the main reasons why paediatric gastroenterologists have become increasingly interested in non-invasive means of assessing gastrointestinal motility and transit. Such techniques include radionuclide scan (scintigraphy), ultrasonography, breath test and electrical impedance tomography for the study of gastric emptying and the recording of electrical activity of the gastric antrum by surface electrodes, i.e. electrogastrography or EGG.

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Physiology of Gastric Motility and Gastric Emptying

The stomach has a rather sophisticated and diversified motor function (Fig. 114.1). The fundus provides receptive relaxation to accommodate food, and low-frequency tonic contractions provide a pressure gradient that facilitates the aborad progression of the bolus. In the proximal corpus, a specialised region where interstitial cells of Cajal are concentrated acts as a pacemaker originating regular 0.5 Hz (3 cycles/min) electrical activity. This activity sweeps all the way down and around the stomach due to the syncytial structure of the longitudinal, circular and oblique smooth muscle layers of the gastric wall. This pacemaker activity underlies the strong peristaltic contractions of the distal corpus and antrum that are responsible for mixing, grinding and propulsion of food, as well as clearing of gastric residues during phase III of the migrating motor complex. The pyloric region is characterised by coordinated contractions that control gastroduodenal flow. Gastric emptying, however, is not just a mechanical event, since it is modulated by central influences (cephalic phase of digestion) and several intraluminal factors such as the caloric content, osmolarity and composition (medium- or long-chain triglycerides, type of carbohydrates, protein source) of the meal (Figs. 114.2, 114.3, 114.4, 114.5, 114.6 and 114.7).

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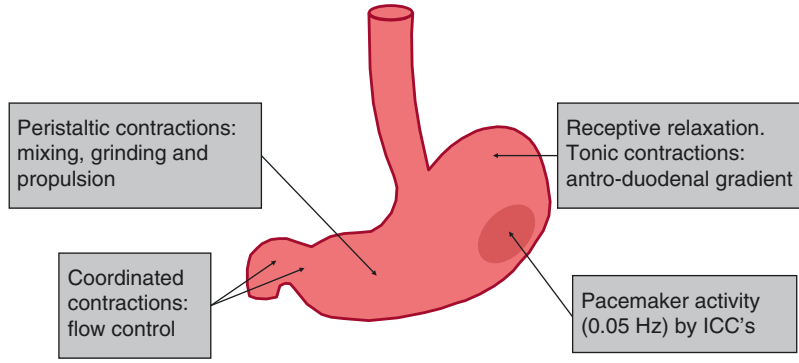
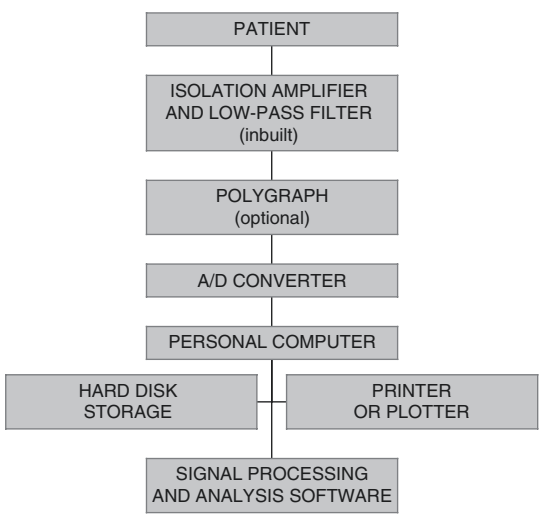


Fig. 114.1 Motor function of the normal stomach



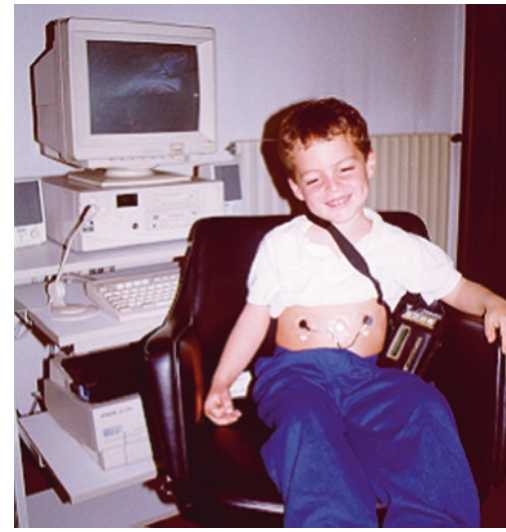


Fig. 114.2 Electrogastrography (EGG) in action with the data flow IT (fast Fourier transform, autoregressive modelling/exponential distribution)

Electrogastrography (EGG)

History of the EGG

From a historic point of view, EGG is not new in paediatrics. Back in 1926, in fact, 4 years after the first description of a human EGG by Walter Alvarez, I. Harrison Tumpeer, a paediatrician, published an article on the "registration of peristalsis by the Einthoven galvanometer" [1], and a few years later, Tumpeer and Phillips reported the successful recording of an EGG from a 5-week-old infant with pyloric stenosis [2], who was so thin that gastric peristalsis was evident by simply watching the skin over his abdomen. It is noteworthy that this tracing (obtained by using standard ECG limb leads) was described by the authors as looking like an ECG with a slowly changing baseline. The changes in the baseline clearly occurred at approximately 0.05 Hz and closely matched the frequency of gastric contractions that could be observed visually. Therefore Tumpeer and Phillips suggested that such ECG baseline changes, which had often been reported (but not explained) by cardiologists, were in fact due to gastric peristalsis. Since then, there were

no further EGG studies in paediatric patients until 1978, when Telander et al. published a report describing a small infant with severe intractable vomiting and a marked impairment of gastric emptying. These abnormalities were related to a severe dysfunction of gastric smooth muscle, which in turn was due to a derangement of the frequency of gastric electrical control activity from the customary 3 cpm to a "tachygastria" of 4.7 cpm, and to an orad propagation of the electrical activity recorded in the gastric antrum [3]. A similar patient with tachygastria underlying an intractable vomiting and the inability to assume oral feeds was described a few years later by Cucchiara et al. [4]. In both these patients, antrectomy was curative of vomiting and gastroparesis and allowed the children to resume oral feeds.

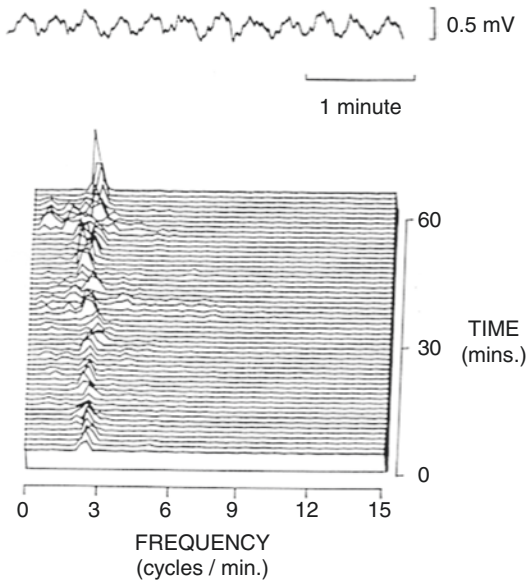


Fig. 114.3 Normal 3 cycles per minute gastric contractions with amplitude on the z axis

Recording and Analysis of the EGG

With time, the technique of recording and evaluation of the gastric electrical activity from surface electrodes has been considerably improved. The use of bipolar electrodes, adequate amplifiers and band-pass filters allows the recording of a much clearer signal. The digital conversion of the raw analogue signal at frequencies of 1–5 Hz provides a mathematical representation of the signal which is suitable for subsequent computerised analysis. The technique of running spectral analysis [5] (by fast Fourier transform, autoregressive modelling or exponential distribution) [6] allows the frequency and power of the signal to be assessed in a more objective fashion than the simple visual inspection. Also, recent developments such as the wavelet analysis [7] can be used to remove artefacts and improve the interpretation of the recording, especially in infants and young children. Such techniques are now customary in modern EGG and were used in a number of paediatric EGG studies that have appeared in the literature over the last 20 years. Essentially, these studies were aimed at either

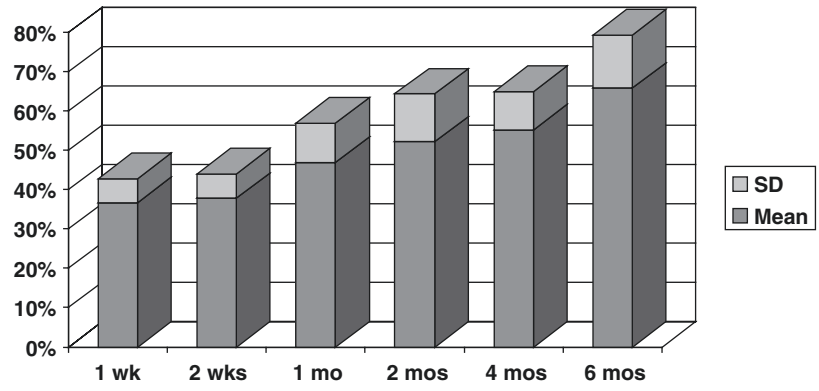


Fig. 114.4 As infants mature the frequency of 2–4 contractions per minute (cpm) increases until at around 4–5 months of age these account for approximately 70 %

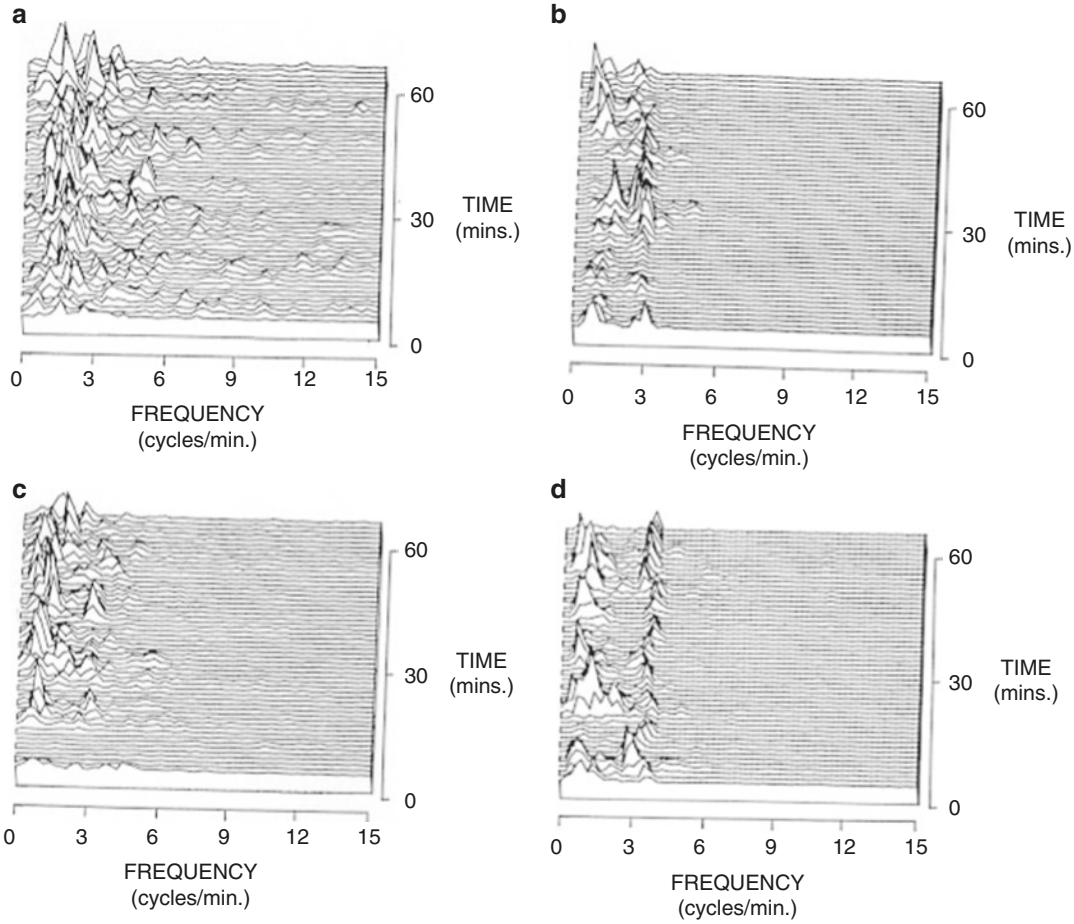


Fig. 114.5 Pre- (*left*) and post- (*right*) prandial gastric EGG both of which can be affected by intra-luminal contents including the caloric content, osmolarity and composition (medium- or long-chain triglycerides, type of carbohydrates, protein source) of the meal

defining the ontogenesis and development of gastric electrical control activity or at investigating the role of gastric antral dysrhythmias in a number of paediatric disorders characterised by nausea, vomiting and feeding problems.

Ontogenesis and Development of Gastric Electrical Activity

Koch et al. found a considerable degree of instability in the postprandial gastric electrical activity of both preterm (28–32 weeks) and term babies, with normal 2.5–3.6 cpm frequency occurring only for 9–34 % of the time and being often overwhelmed by frequencies within the bradygastria or tachygastria range [8]. On the other hand, premature babies did not exhibit any increase in EGG power after gavage feeding of a standard low-birth-weight formula. These findings may reflect an immature response of the gastric neuromusculature (and also of the humoral control system) to formula feeds. Zacchi et al. described cyclic frequency changes of gastric electrical activity in term as well as preterm infants, with faster changes in the latter [9]. Interestingly, Mihailoff et al. reported movement artefacts as a major cause of unusual distribution of frequency and amplitude of the EGG signal in as many as 51 % of infants [10]. This is a common experience for paediatricians involved with gastrointestinal motility testing and should be

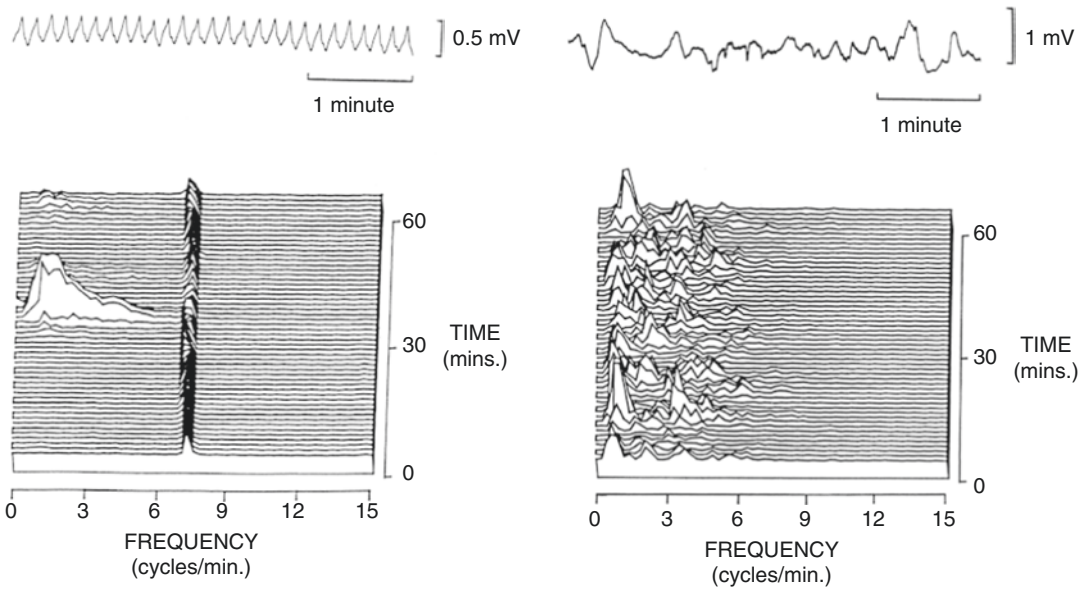


Fig. 114.6 An example of tachygastria (*left*) and disordered gastric contraction frequency (*right*)

taken into account in order to avoid an overestimation of gastric dysrhythmias. By carrying out consecutive measurements of the EGG (at 1 week and 2 months), Liang et al. were able to describe a developmental pattern of gastric electrical activity in preterm infants, which was characterised by a significant increase in the percentage of 2–4 cpm activity and a reduction or normalisation of tachygastria [11]. Furthermore, by the age of 4.5 months, full-term infants showed a significantly higher (70 %) percentage of regular 3 cpm gastric slow waves in comparison with premature babies.

EGG in Clinical Practice

Severe Disorders of Gastrointestinal Motility

A number of EGG studies have been carried out over the years in children with different disorders affecting all the control levels of gastrointestinal motor activity: myogenic, neurogenic (intrinsic and extrinsic) and humoral. Children with chronic intestinal pseudo-obstruction related to a primary neuromuscular disease of the gut may exhibit two distinctive patterns of gastric dysrhythmias: children with an enteric myopathy did have a continuously irregular gastric electrical activity where no dominant frequency could be detected, whereas children with histologically proven neuropathic disease had a persistent tachygastria [12]. Several factors may account for the unstable electrical activity found in patients with myopathy: the inability to maintain a constant frequency or a poor summation of the electrical signal, due to a patchy involvement of smooth muscle cells and/or interstitial cells of Cajal in the disease process, or a marked reduction in signal amplitude and thus in signal-to-noise ratio. On the other hand, the most likely explanation for the tachygastria found in children with enteric neuropathy is a lack of intrinsic inhibitory innervation. Using techniques of chaos analysis, the presence of complex high-dimension interactions in the EGG of children with myopathic pseudo-obstruction was demonstrated, suggesting that gastric myocytes behave like other excitable cells, interacting in a chaotic manner that is increased by disease [13].

Neurological Disorders

Severe recurrent vomiting, often complicated by aspiration and failure to thrive, is common in children with disorders of the central nervous system (CNS) such as cerebral palsy and psychomotor

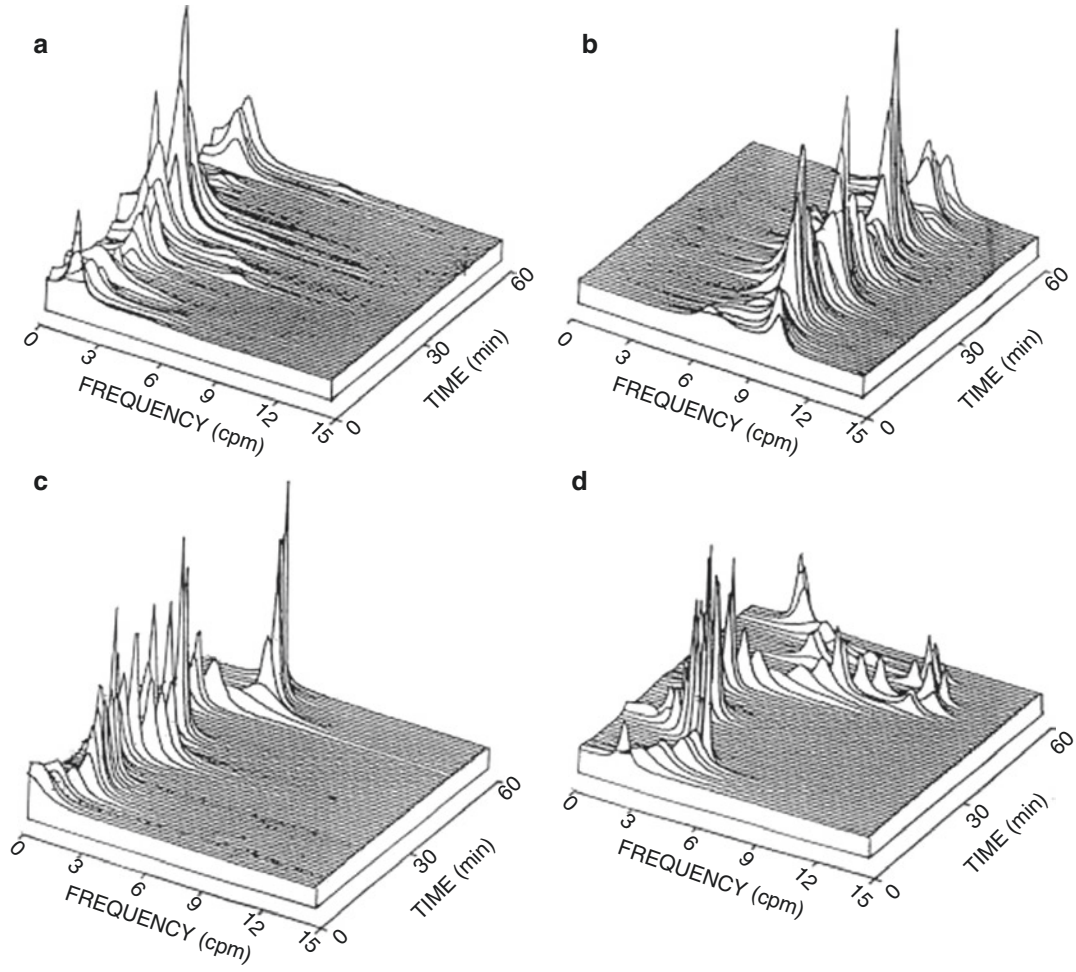


Fig. 114.7 Examples of high amplitude gastric dysrhythmias including abnormal post-prandial tachygastria

retardation. Vomiting is usually ascribed to gastro-oesophageal reflux, which indeed can be found in about 75 % of these patients. In vomiting children with cerebral palsy and neurodevelopmental delay, the majority of whom had gastro-oesophageal reflux, gastric dysrhythmias of different sorts (tachyarrhythmia, bradyarrhythmia, mixed dysrhythmia or unstable electrical activity) were as common as gastro-oesophageal reflux, occurring in 62 % of the patients and were associated with reflux in one-third of them [14]. Furthermore, gastric dysrhythmias were present in most children with disorders of the CNS who had persistent retching and postprandial discomfort following Nissen fundoplication and were already present before the procedure was carried out [15]. Thus it appears that children with CNS disease who suffer from recurrent vomiting often have a widespread disorder of foregut motility, where gastric dysrhythmias (possibly due to persistent activation of the emetic reflex) are as common as – and may contribute to – gastro-oesophageal reflux. In these children gastric dysrhythmias are probably due to abnormal modulation of the enteric nervous system by the CNS, although in some cases an involvement of the enteric nervous system by a process similar to that affecting the brain cannot be excluded.

Postsurgical Nausea and Vomiting

As mentioned above, gastric dysrhythmias were found in children with CNS disorders who had persistent retching following Nissen fundoplication [15, 16], and in the majority of them, dysrhythmias were already present before the procedure was carried out [16]. Since gastric dysrhythmias may be unmasked by Nissen fundoplication, EGG can be useful in detecting which patients are more likely to have retching problems following this operation, so that in these patients alternative therapeutic interventions may be considered [15–17].

Vomiting, retching and feeding difficulties are often present in children who underwent oesophageal replacement for complex oesophageal malformations (e.g. oesophageal atresia with or without tracheo-oesophageal fistula or extensive peptic/caustic stricture) [18]. In a group of 12 such children who had been subjected to gastric transposition, the emptying of the transposed stomach varied – delayed in 7, accelerated in 4 – but in the 4 who had dumping-like symptoms, the EGG looked entirely normal [19].

Disorders of Eating Behaviour

Gastric dysrhythmias have been described in adults with anorexia nervosa [20]. In children with early-onset anorexia nervosa, on the contrary, the frequency of fasting and postprandial electrical activity and the fasting/postprandial amplitude ratio did not significantly differ from that of controls, although patients with longer established disease had a smaller increase in amplitude [21]. It is therefore possible that gastric motility disturbances detected in adult patients with anorexia nervosa are related to a longer duration of the disease and are a consequence, rather than a cause, of malnutrition in these patients.

Functional Gastrointestinal Disorders

Different gastric dysrhythmias and delayed gastric emptying of a mixed solid-liquid meal have been reported in a high proportion of children with non-ulcer dyspepsia [22–24]. In a few patients, these alterations, together with the clinical symptoms, were successfully treated by the prokinetic drug cisapride [23]. It is interesting to note that in many children with non-ulcer dyspepsia, no significant correlation was found between gastric dysrhythmias, gastric emptying and the patients' symptom score [25, 26].

Similarly to other functional GI disorders, gastric dysmotility and the related symptoms of nausea, vomiting and gastric retention can be a consequence of a gastrointestinal infection [27, 28]. Indeed gastric dysrhythmias have been found in patients who developed gastroparesis following a viral gastroenteritis [27, 29] as well as dyspeptic patients with chronic gastritis due to *Helicobacter pylori* [30, 31], with the former condition being self-limiting in most cases and the latter usually resolving after successful eradication therapy [27–31]. Studies in animal models suggest that *H. pylori* infection may induce dyspeptic symptoms via a complex sensory-motor dysfunction of the enteric nervous system [32].

Chronic Renal Failure

A number of neuroamines (e.g. noradrenaline or dopamine) and polypeptide hormones (e.g. gastrin, glucagon, cholecystokinin) have the potential to induce gastric dysrhythmia, delayed gastric emptying, nausea and vomiting in experimental animals as well as in humans [33–35]. The effects of an altered humoral environment on gastrointestinal motility were investigated in children with chronic renal failure, in whom the metabolism of several polypeptide hormones is impaired [36]. Those children who suffered from anorexia, nausea and vomiting were found to have dysmotility of the foregut in the form of gastro-oesophageal reflux, gastric dysrhythmia and/or altered gastric emptying [37, 38]. In most of them, serum levels of gastrin were increased above the upper normal limit [37]. In subsequent studies, vomiting and anorectic children with chronic renal failure were found to have significantly higher fasting and postprandial serum levels of gastrin, cholecystokinin and neurotensin compared to asymptomatic uremic children and children who had undergone renal transplantation [39]. On the other hand, motility tests were

normal in asymptomatic children with renal failure [38]. Following renal transplantation, the gastric dysrhythmias disappeared in all patients in whom renal function and polypeptide hormone levels had normalised [36, 38, 39]. Thus it appears that gastric dysrhythmias (and gastro-oesophageal dysmotility in general) in chronic renal failure are related to an altered humoral environment generated by the impaired renal degradation of these polypeptide hormones.

Food Allergy

Gastric dysmotility and upper gastrointestinal symptoms can be related to food hypersensitivity. Gastric dysfunction in food allergy is described in detail in the next chapter.

Gastric Pacing

Conclusion

In summary, gastric motor function is subjected to complex control mechanisms, and gastric dysmotility is present in a wide variety of paediatric disorders characterised by symptoms of nausea and vomiting where such control mechanisms are deranged. EGG can be safely and effectively used in paediatric patients, from premature babies to children and adolescents, to investigate the ontogenesis of gastric electrical activity and the pathophysiology of gastric dysrhythmias in children with vomiting and feeding disorders. In analogy to other aspects of gastrointestinal motility such as lower oesophageal sphincter pressure and small intestinal motility, gastric antral electrical activity appears to develop from the prenatal period through the first few months of life. In normal healthy children, gastric electrical activity is similar to that in adults in terms of both frequency and response to a meal. Relevant abnormalities (gastric dysrhythmias) have been detected and characterised in several conditions where the different control levels of gastric motor activity are affected, although the correlation between myoelectrical disturbances and gastric motility and emptying is not always clear. Recent developments such as electrical pacing, prolonged ambulatory EGG monitoring, chaos analysis and spatial mapping of gastric frequencies should render the EGG more and more meaningful for the study of gastrointestinal pathophysiology and the assessment of gastrointestinal motility disorders.

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Part XXI

Anatomical Gastropathology

Anatomical Gastropathology

115

Basil Bekdash and Sean S. Marven

General

At first glance, the stomach appears to be a simple organ but this belies its functional complexity and importance in normal eating behaviour. In modern societies with abundant calorific foodstuffs, it is arguable that the stomach's adaptability and effectiveness in handling dietary intake permits the increasing prevalence of obesity. Anatomical abnormalities will often produce dramatic and acute but non-specific symptoms.

The stomach is a robust and accessible organ with a rich blood supply from all three main branches of the coeliac artery as well as extra-axial vessels. This affords endoscopists and surgeons multiple options in approaching anatomical pathologies.

As discussed (section "Gastric Volvulus"), the stomach is first discernable as a dorsal foregut expansion in the fourth/fifth week of embryogenesis [55]. Deviations from the typical developmental programme may produce anatomical variants and anomalies that cause symptoms or are detected incidentally during radiological, endoscopic or surgical evaluation. When managing these conditions, caution should be exercised as the majority are rare and variable entities frequently associated with other significant anomalies.

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Congenital Gastric Abnormalities

The majority of anatomical abnormalities of the stomach are in some sense congenital though many do not present until some time after birth. Occasionally lesions may be suspected antenatally, though the features are non-specific (absent stomach, dilated stomach) and are more likely to be due to commoner anatomical anomalies such as oesophageal atresia and duodenal atresia, respectively.

Outlet Obstruction

The presentation will depend on the degree and frequency (when intermittent) of obstruction and the age at onset for acquired causes. Invariably there will be non-bilious vomiting which may be intermittent if the obstruction is incomplete or intermittent as occurs with some antral webs and duplications. Vomiting secondary to high gastrointestinal obstruction will variably result in failure to thrive, dehydration and the classical hypochloremic hypokalaemic metabolic alkalosis (section "Infantile Hypertrophic Pyloric Stenosis") in severe or chronic cases. Pyloric atresia is the archetypical congenital anatomical cause of gastric outlet obstruction though at least some cases of gastric antral web appear to be congenital, and hypertrophic infantile pyloric stenosis may rarely present at birth [71] (and personal experience).

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Pyloric Atresia

Pyloric atresia is a rare disorder in which there is congenital discontinuity of the gastrointestinal lumen at the level of the pylorus. The quoted incidence of 1/100,000 [40, 48] is based on German studies from the 1970s [2, 18] and a presumption that pyloric atresia represents 1 % of all gastrointestinal atresias. The anomaly has been subdivided based on the morphology of the atresia in a similar manner to other gastrointestinal atresias: type I/A ('membrane') have a thin membrane or web obstructing the lumen. This can result in a so-called windsock deformity, commonly seen in membranous forms of duodenal atresia. In type II/B ('atresia'), the pylorus is in continuity with the duodenum but the lumen is obliterated for a variable distance. In the least common type III/C atresia ('aplasia'), the pylorus is completely dissociated from the distal gastrointestinal tract [48].

The embryopathogenesis is unknown though a first trimester insult is often postulated, largely based on the known associated anomalies rather than any mechanistic hypothesis [2]. There is a well-documented incidence of pyloric atresia with certain forms of epidermolysis [18, 23, 44]. Epidermolysis has been specifically implicated in the coexistence of pyloric and oesophageal atresia and was found in 25 % of 140 cases in the largest (and under cited) series [56]. Epidermolysis associated with pyloric atresia has been described in several syndromic forms and with a variety of other non-cutaneous manifestations (ID #612138, ID#226720) [1, 53]. Gene defects associated with epidermolysis bullosa (simplex)-pyloric atresia (EB(S)-PA) have been identified and affect cell adhesion molecules: plectin 1 (~5 %), integrins α6 (~15 %) and β4 (~80 %). Defects in integrin β4 associated with pyloric atresia and other gastrointestinal manifestations have been found in the absence of cutaneous involvement [57].

Congenital pyloric atresia presents soon after birth with non-bilious vomiting, but the diagnosis is often delayed, allowing fluid and electrolyte disturbances to develop which should, as always, be judiciously corrected. The classical radiographic finding is of a 'single bubble' representing the postnatally gas-filled and distended stomach (Fig. 115.1). The membrane in type I atresia may bulge into the duodenum and can mimic the radiographic 'double bubble' seen in duodenal atresia [50]. Occasionally the newborn will present with gastric perforation secondary to acute gastric distension [7]. Associated anomalies should be excluded by family history (for epidermolysis in particular), general clinical examination and imaging (echocardiogram, renal ultrasound). Malrotation and absent gall bladder have also been associated and can be excluded during the surgical repair of the atresia [2, 44, 48]. Other gastrointestinal atresias occurred in

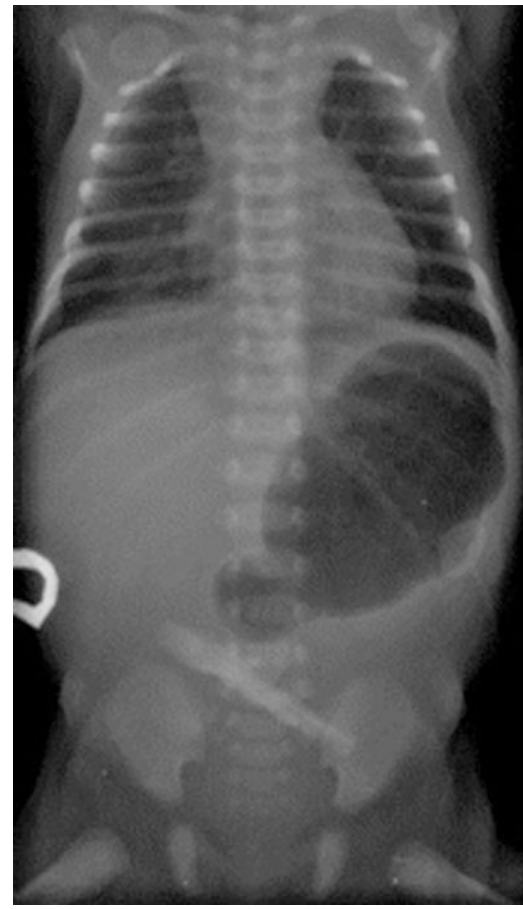


Fig. 115.1 Typical 'single bubble' radiographic finding in pyloric atresia (Reproduced with permission from Darwish et al. [11])

10 % of the largest series [56] and this possibility should be considered.

Gastrojejunostomy where it has historically been performed has had a poor outcome [28]. Primary restoration of continuity of the stomach and duodenum by excision of the web and pyloroplasty (Finney or Heineke-Mikulicz) in type I atresias and excision with primary gastroduodenal anastomosis in type II and III atresia is currently recommended [2, 23, 40, 48]. The outcome of pyloric atresia in isolation is generally believed to be good, and it is the associated anomalies that determine the longer-term prognosis, producing a relatively high mortality in some series [23]. The relative rarity of the disorder and the common association with other anomalies make further generalisation difficult. Reporting in the literature has been sporadic at best.

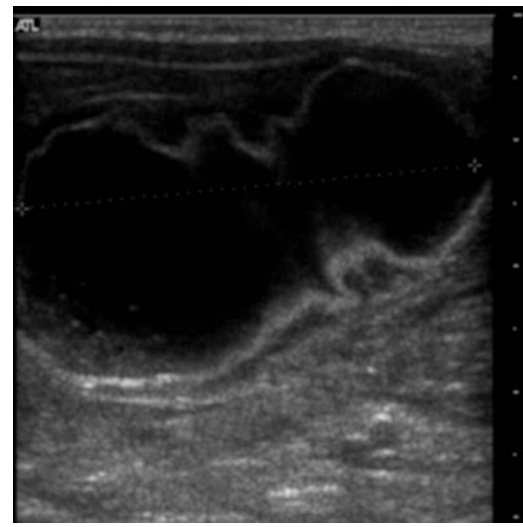
Antral Web

The antral or prepyloric web is an unusual and incompletely defined entity. It has been described in newborns [52], where it must presumably be congenital, as well as in older children and adults where in some cases it was radiologically documented to arise de novo [22]. Whether the two entities are related is unclear, but they show histological similarity, consisting of normal mucosa overlying submucosa and muscularis [42]. This is akin to a similar entity in the small and large intestine (the so-called diaphragm disease [31]) and the normal structure of the plicae circulares. In adults, acquired antral webs and the mucosal diaphragms of diaphragm disease have been postulated to develop in response to mucosal injury and have been related to peptic ulceration [22] and chronic NSAID use [20], respectively.

In infants, the presentation is with incomplete gastric outlet obstruction that may mimic hypertrophic infantile pyloric stenosis (IHPS). The diagnosis may be made on ultrasound but is more likely with an upper gastrointestinal contrast study. Antral web has occasionally been reported in association with IHPS [37]. Treatment in symptomatic cases consists of web excision by endoscopic [36], open [33] or minimally invasive surgery but will depend on the size of the patient, available equipment and expertise. Cases of acquired antral web and diaphragm disease in adults without complete obstruction have been managed medically, directed at the presumed cause of mucosal injury. Empirical removal of risk factors for mucosal injury in either case is sensible after excision to limit recurrence. There have been no long-term studies of outcomes following any intervention owing to the relative rarity of the condition in childhood.

Gastrointestinal Duplications

Gastrointestinal duplications may be cystic or tubular and occur in all parts of the gastrointestinal tract from oesophagus to rectum [61, 62]. They are typically closely related to and share a common wall with the primary gastrointestinal tract, having the same characteristic ultrasonographic appearance (Fig. 115.2). Tubular duplications are more likely to communicate with the primary tract than cystic forms and can be extensive [26]. A few reports of cysts with no direct connection to the primary tract but histological



Fig, 115.2 Sonographic appearance of a pedunculated cystic duplication arising from the posterior gastric wall. Note the characteristic gastrointestinal wall three-layer sonographic signature

features consistent with gastrointestinal duplication have been published [34, 59].

The diagnosis is frequently incidental and may be made late in adulthood [30] typically after imaging (ultrasound or cross-sectional) in the investigation of unrelated symptoms. Symptomatic duplications cause mass effect [51], gastrointestinal bleeding or pain secondary to ulceration caused by ectopic gastric-type mucosa [62] and infection via communication with the primary tract or after bacterial translocation [24]. Gastric duplications represent a minority of all gastrointestinal duplications (5-10% [62]) and typically present incidentally or as a cause of gastric outlet obstruction [51].

Management is determined by the anatomical location, morphology and any symptoms or secondary effects caused by the duplication. Gastric duplications can usually be excised with relative ease by open or minimally invasive approaches [14] occasionally requiring entry to the lesser sac between the transverse colon and greater curve when they arise from the posterior wall of the stomach. Gastric duplications communicating with the pancreatic ductal system [45, 69] require an approach tailored to the individual anatomy to ensure management is safe and effective. This may entail excision of accessory pancreatic tissue or Roux-en-Y drainage [45]. Thorough preoperative planning and intraoperative caution are advised to avoid complications due to unexpected anatomy. Endoscopic resection of predominantly intraluminal lesions has been reported in adults [60] but again requires careful pre- and peri-procedural evaluation to limit the risks of incomplete resection and perforation.

Short-term complications for simple duplications are limited to the general complications of surgery and leak from the suture/staple line (unusual from the stomach). The long-term prognosis is excellent if excision is complete and particularly for asymptomatic simple duplications, a minimally invasive approach is ideal where skills and technology permit. There may be additional sequelae where the lesion is closely related to the pancreas or pylorus and a more complicated reconstruction is performed.

Microgastria

Microgastria is an even rarer entity than pyloric atresia with less than 100 reported cases in the English language literature. There is no strict definition and congenital microgastria is diagnosed when there is the impression of an exceptionally small stomach, often so rudimentary as to be difficult to distinguish from the adjacent normally tubular foregut elements (Fig. 115.3). Small stomachs are a recognised consequence of gastrointestinal obstruction proximal to the stomach most commonly seen in pure oesophageal atresia. This is not usually termed microgastria but is plausibly presumed to be due to the absence of intrauterine gastric filling by swallowed amniotic fluid. The situation is complicated by cases of 'true' microgastria associated with oesophageal atresia and the frequent association of microgastria with conditions that might reasonably be expected to impair swallowing (Pièrre-Robin sequence [17, 32], laryngotracheal clefts [27, 67], severe CNS abnormalities).

The association of microgastria with upper limb reduction defects is perhaps the most formally documented (MIM ID 156810) [1] but is perhaps no stronger than with, for example, splenic malformations and other major foregut

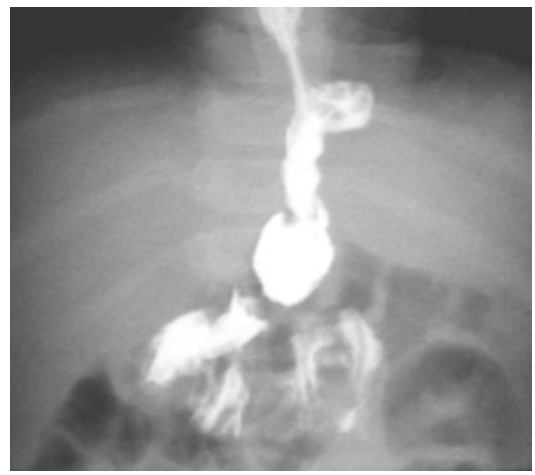


Fig. 115.3 Upper gastrointestinal contrast study demonstrating typical appearance of microgastria (Reproduced with permission from Dr DH Jamieson, Dept Radiology, British Columbia Children's Hospital, Canada)

deformities. The spectrum and severity of anomalies does suggest an early defect in embryogenesis as many have speculated. Apparently isolated microgastria has only been reported in a handful of cases presenting with feed intolerance and failure to thrive though in these cases the patients had reached several months of age [39, 54].

Given the nature of the associations of the condition, surgical reconstruction has only been performed in a minority of cases [25, 39, 54]. Published cases suggest, perhaps surprisingly, that an expectant management approach awaiting feed-related gastric expansion is ineffective and potentially dangerous given the propensity for gastro-oesophageal reflux-associated aspiration in this patient group. There have been no documented cases of attempted staged gastric expansion.

Surgical reconstruction, when performed, has been by augmentation of the micro-stomach with a jejunal J-pouch and Roux-en-Y anastomosis [12, 66], attributed to Hunt and Lawrence who described it for postgastrectomy reconstruction (Fig. 115.4). Long-term results in the survivors have been reportedly good with tolerance of a normal diet [25]. With such small case numbers, generalisations are impossible more so with this complex and varied patient group. Individualised multidisciplinary care is mandatory with careful selection of patients for gastrointestinal reconstruction preceded by thorough preoperative planning and investigation of associated anomalies.

Infantile Hypertrophic Pyloric Stenosis

Infantile hypertrophic pyloric stenosis (IHPS) is the commonest anatomical gastric lesion occurring in childhood, with an estimated incidence of 2–5 per 1,000 live births in Western populations.

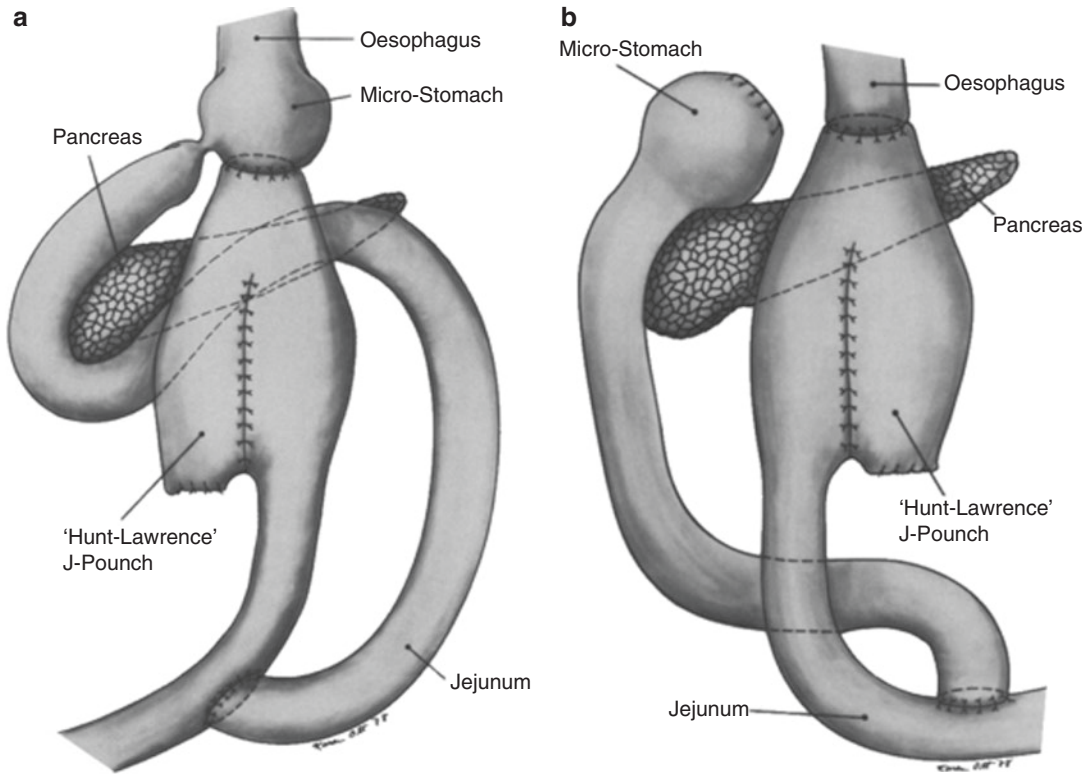


Fig. 115.4 Two options for gastric augmentation ('Hunt-Lawrence' pouch) with stomach in situ (**a**) and with gastric disconnection (**b**) (Reproduced with permission from [66])

The incidence in Afro-Caribbean and Asian populations is generally considered to be lower [35]. For reasons that remain obscure, the pyloric smooth muscle hypertrophies and enters a state of chronic contraction at some time after birth. There is a striking but unexplained male preponderance (consistently 4:1). Maternal risk transmission and familial cases suggest a partly genetic aetiology, though twin and sibling studies contradict this [43]. No single gene defect has been identified to date and work on susceptibility loci as well as candidate susceptibility genes such as nNOS is incomplete [49].

Non-bilious vomiting is invariable and classically becomes projectile, a term that has become synonymous with the condition. The severity of symptoms and biochemical derangement is variable, and it is plausible that 'subclinical' cases may exist. The advent of reliable ultrasound diagnosis is changing the pattern and time of diagnosis but potentially creates new diagnostic challenges [41, 46]. It has long been known that IHPS will clinically resolve with time and histological regression has also been demonstrated [65]. Medical treatment has been advocated particularly in the Far East (principally with atropine [21]) but is incompletely effective, requires longer admission and is not routinely practised in Western healthcare systems as a consequence.

The safe surgical treatment of IHPS is critically dependent on adequate preanaesthetic resuscitation and biochemical normalisation. The persistent and severe vomiting that usually develops produces a classical electrolyte disturbance (common to all causes of high gastrointestinal obstruction) in addition to the features of dehydration (rarely with shock) and under nutrition. In addition to reduced fluid and electrolyte absorption, water, sodium and chloride are all lost directly from the stomach because of vomiting. There is further compensatory renal loss of potassium and hydrogen ions with increasing severity until the classical hypochloraemic, hypokalaemic metabolic alkalosis is fully developed. With earlier presentations, the capillary blood gas may be normal or show only compensatory elevation in the bicarbonate/base excess.

Following resuscitation, the chronic electrolyte and fluid depletion must be corrected at a safe rate for which numerous protocols exist. All follow the basic principle of providing maintenance requirements, replacing the deficit and compensating for any additional ongoing losses. This is continued until biochemical restitution [70] at which point the risks of anaesthesia and thus surgery are minimised. The principle risk, apnoea, is generally held to be related to reduced central respiratory drive secondary to (CSF) alkalosis and can occur spontaneously preoperatively [16].

Surgery for IHPS has been performed for over a century, and the core therapeutic intervention, namely, extramucosal pyloromyotomy, has remained largely unchanged. The mode of access to the pylorus has evolved from laparotomy (typically via a transverse right upper quadrant incision) to a more cosmetic supraumbilical incision [64] and since the 1990s [3] to various laparoscopic approaches. Our preferred approach is via open transumbilical insertion of the primary (camera) port and two 3 mm stab incisions for the (portless) working instruments. The pylorus is superficially incised with an SM69 blade (Swann-Morton, Sheffield, England, UK) and split with a 3 mm laparoscopic pyloric spreader (Fig. 115.5). This simple, reproducible and safe method optimises the utility and cosmesis of the laparoscopic approach. A recent systematic review [58] identified only five studies of level 2 or higher evidence comparing open supraumbilical and laparoscopic approaches and concluded the outcomes were broadly similar with some evidence of benefit in the laparoscopic group in terms of wound-related complications. There was some evidence of quicker time to full feeds; however the small magnitude of the effect, multiple confounders and other statistical irregularities have made this a more contentious finding.

Following uneventful surgery, feeds can be reintroduced as the infant tolerates with close initial monitoring for evidence of undetected perforation. Perforation and incomplete myotomy are the primary specific risks of surgery and occur in <2 % of cases [58]. The reported incidence varies and is biassed by the relatively small sample sizes in published series/studies. Other risks include

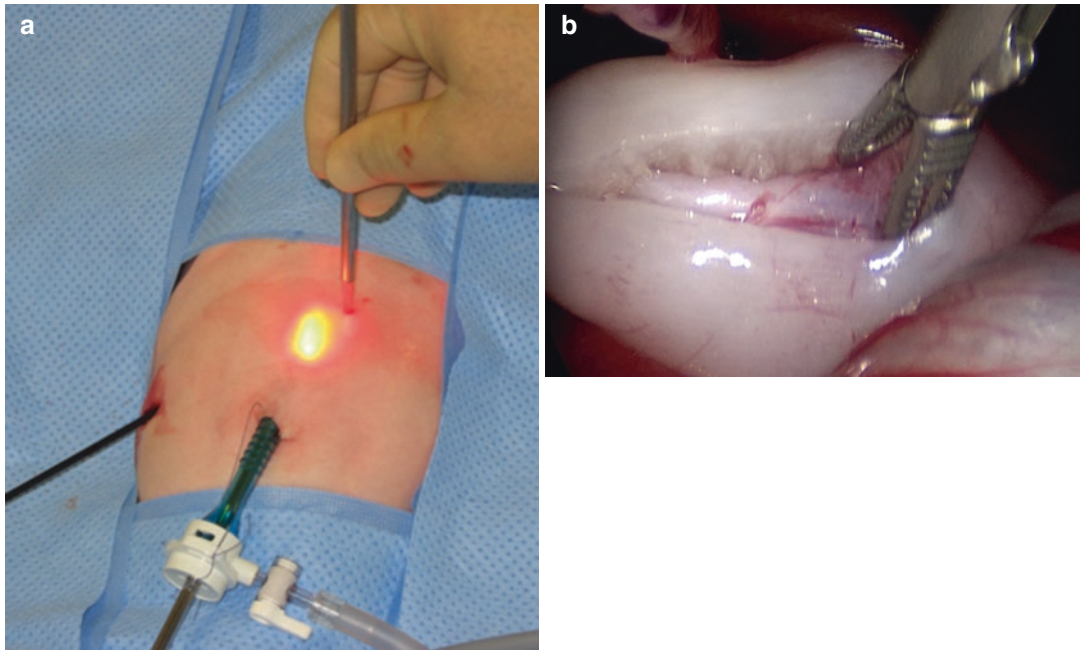


Fig. 115.5 Laparoscopic pyloromyotomy: (**a**) Our institutional intraoperative setup: transumbilical camera port, right lateral (atraumatic grasper) and epigastric (myotomy blade and spreader) portless instruments. Myotomy blade in use. (**b**) Intra-abdominal appearance during pyloric spreading demonstrating split pyloric muscle and bulging mucosa

wound infection, port site herniation and anaesthetic-related events (e.g. apnoea, aspiration).

The long-term outcomes after surgery for IHPS are believed to be excellent but published data is limited in scope. There is some recent and ongoing work suggesting minor adverse effects on neurodevelopmental outcomes compared to matched controls [68]. The origin of this effect is not known but if genuine may be related to general anaesthesia as suggested recently in the anaesthetic literature [63]. This is currently the subject of intense debate and clearly has wider implications.

Gastric Volvulus

Gastric volvulus is defined by both its morphology and clinical time course (acute, acute-on-chronic, chronic). It has been distinguished from gastric torsion by the degree of twisting (volvulus being a rotation of >180°) and the consequent relative symptom severity [9]. Morphological classifications of gastric volvulus inform the radiographic and operative appearances, and the configuration is determined by the specific anatomy in each case. The axis of rotation can be organoaxial, mesenteroaxial or mixed (Fig. 115.6). Historically considered a rare entity [6, 19], a recent review of published cases [9] has suggested gastric volvulus is commoner than suspected. The discrepancy in case numbers identified by reviewers writing at similar times suggests an inconsistency of definition arising from the broad spectrum of predisposing factors.

The normal stomach is fixed at the gastro-oesophageal junction and pylorus at the gastrointestinal tract becomes retroperitoneal. Excess movement is limited by the peritoneal attachments of the stomach derived from the embryonic ventral and dorsal mesentery (gastrohepatic, gastrophrenic, gastrocolic and gastrosplenic 'ligaments'). Primary gastric volvulus occurs in the absence of other gross anatomical anomalies and is attributed to congenital or acquired laxity of

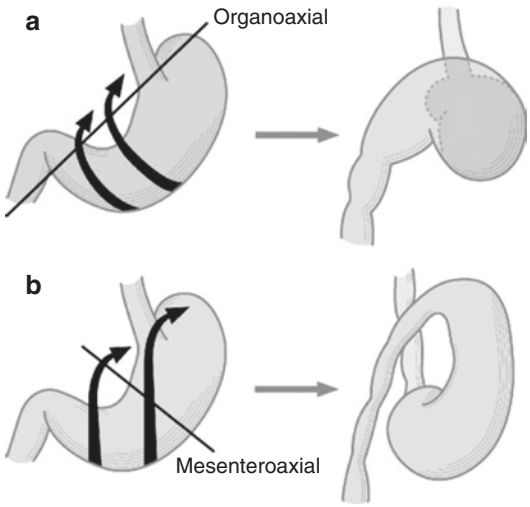


Fig. 115.6 Diagrammatic representation of two axes of gastric volvulus (a = organoaxial and b = mesenteroaxial) and typical configuration of volved stomach (Reproduced with permission from Darani et al. [10])

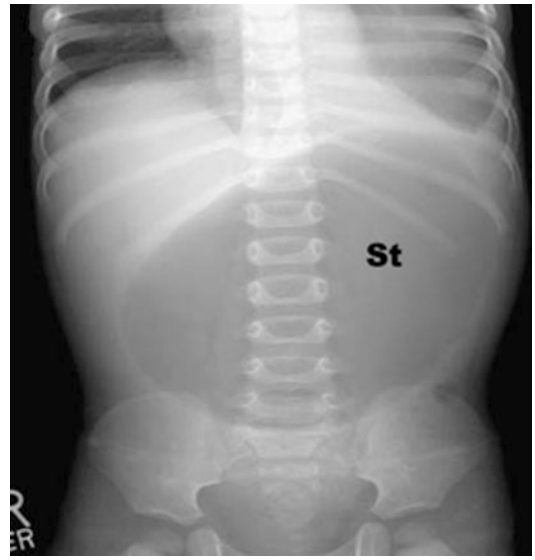


Fig. 115.7 Characteristic radiographic appearance of acute gastric volvulus. In this case, the distension is mild following insertion of a nasogastric tube. Note the absence of distal gas (Reproduced with permission from Oh et al. [47])

these structures. Secondary volvulus occurs either due to congenital or degenerative anatomical defects altering gastric fixation (diaphragmatic abnormalities, asplenia, abnormal gastrointestinal rotation, oesophageal hiatal defects) [9] or to traumatic and surgical disruption of the same structures (e.g. after Nissen fundoplication [29], liver transplantation [15], diaphragmatic rupture [4]).

Acute gastric volvulus in infants and children presents variably with pain (abdominal, epigastric, retrosternal), retching, vomiting, epigastric distension and gastrointestinal bleeding. The commonest (~75%) reported presenting symptom in children is vomiting with other features occurring much less consistently [9]. Approximately 25% of acute cases present with acute physiological (usually respiratory) embarrassment; however, this may reflect the greater prevalence of secondary volvulus in acute cases with diaphragmatic anomalies being the commonest association. In contrast chronic presentations with feed intolerance, intermittent acute symptoms and failure to thrive were predominantly (75%) of a primary nature [9]. Although chronic volvulus has a slight majority of reported cases, it is likely this is an underestimate of the true incidence.

Diagnosis is the first clinical challenge in all cases, largely due to the typically non-specific features even in acute volvulus. Borchardt in 1904 described a classical clinical triad in gastric volvulus: acute gastric distension, retching and the inability to pass a nasogastric tube. The negative predictive value of the triad is questionable, particularly the inability to pass a nasogastric tube. This is not always prevented by volvulus and has been associated with perforation [13, 38]. A specific diagnosis of gastric volvulus will rarely be made during the early assessment, and it is disingenuous to suggest that special care can specifically be taken when passing a nasogastric tube. In the vomiting child with suspected gastrointestinal obstruction, a large bore nasogastric tube should still be carefully introduced, but caution is advised if resistance is encountered.

Management is initially directed at resuscitation and confirmation of the diagnosis, which requires a high index of suspicion in non-fulminant cases. Plain radiography typically shows massive circular gaseous distension (suggestive of an acute-on-chronic pattern) with relative paucity of distal gas (Fig. 115.7 [47]). This is consistent with a closed loop obstruction caused by a valve mechanism at the gastric inlet and

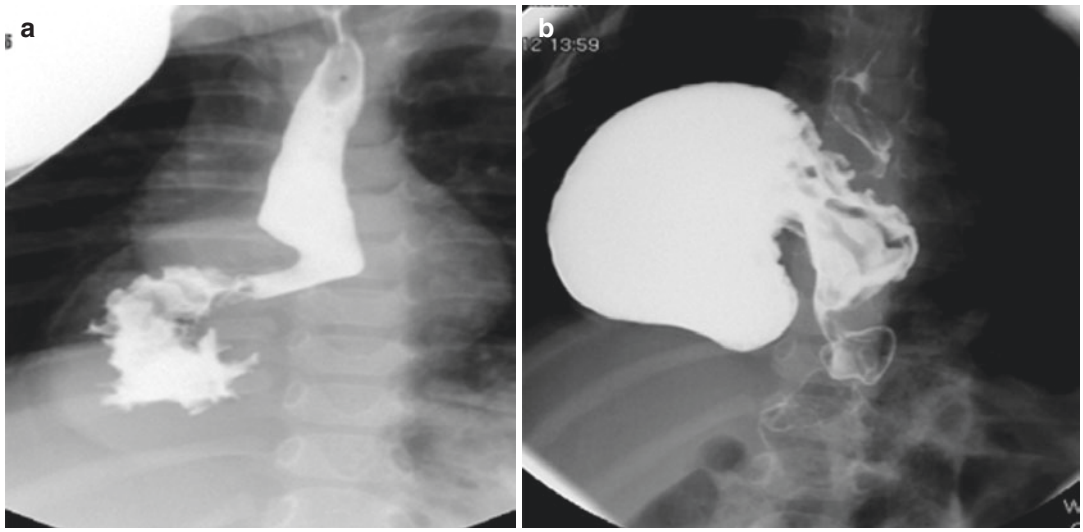


Fig. 115.8 Upper gastrointestinal contrast study demonstrating of organoaxial gastric volvulus during early (**a**) and late (**b**) filling (Reproduced with permission from Dr A Raghavan, Dept Radiology, Sheffield Children's Hospital, UK)

obstruction of the outlet. Upper gastrointestinal contrast studies are the definitive investigation in situations where emergency surgery is not indicated and will demonstrate both the gastric malposition and obstructive effects of volvulus (Fig. 115.8). Gastric volvulus can result in perforation, which can develop rapidly when secondary to massive acute distension or subacutely secondary to ischaemic gastric or distal oesophageal necrosis. In these cases, emergency surgery is indicated and will both confirm the diagnosis and allow for immediate definitive treatment.

There is an incomplete consensus on definitive management, but it is generally agreed that, after derotation and confirmation of viability, any secondary cause should be corrected. This is may be sufficient on its own [5, 9]; however, contrary to this viewpoint, a handful of reports of recurrent volvulus following this approach have been published [8]. Gastropexy can be performed both by open and minimally invasive techniques and by a multitude of techniques. Some authors advocate fixation by gastrostomy tube placement alone; however, gastrostomy tube purely for the purposes of fixation in otherwise healthy patients is probably suboptimal given the possibility of secondary volvulus around a feeding gastrostomy [29]. In keeping with most authorities, we would advocate anterior gastropexy to the anterior abdominal wall as a minimum with additional fixation such as gastrophrenopexy depending on the specific anatomy [5, 9, 10]. With increasing fixation, the consequent distortion of the gastro-oesophageal junction may cause incompetence and additional antireflux procedures may be required [10]. Regardless of the method and adequacy of fixation, recurrence remains a possibility. The true long-term outcomes are not known but are believed to be good in terms of recurrent symptoms or sequelae based on the relatively low frequency of reported complications. Comparison is made difficult by the heterogeneity of the disorder and the complexity of many of the patients' other health and social needs.

There are several unanswered but clinically important questions at this time regarding gastric volvulus. Foremost amongst these is whether gastropexy is mandatory after secondary volvulus noting that this is not routine after, for example, repair of diaphragmatic hernia repair in the neonatal period. Secondly, what is the appropriate threshold for gastropexy in chronic gastric volvulus and even more difficult: is gastropexy appropriate on the incidental finding of risk factors such as diaphragmatic hernia/eventration, asple-

nia, midgut malrotation? Finally, if gastropexy is appropriate, what is the best method in terms of reduced recurrence and side effects such as gastro-oesophageal reflux?

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Congenital Gastric Anomalies

116

Brice A. Antao and Victoria A. Lane

Introduction

Stomach is an embryological derivative of the foregut. The foregut, midgut and hindgut are distinguished on the basis of their blood supply from the celiac trunk, superior mesenteric artery and the inferior mesenteric artery, respectively. At the end of the fourth week, almost the entire abdominal gut tube (portion within the peritoneal cavity, from the abdominal oesophagus to the cloaca) hangs suspended on a dorsal mesentery. In the stomach region, the gut tube remains connected to the ventral body wall by the thick septum transversum. By the fifth week, the caudal portion of the septum transversum thins to form the ventral mesentery connecting the stomach and developing liver to the ventral body wall [32]. On day 26, the thoracic foregut elongates rapidly. Over the next couple of days, the presumptive stomach expands into a fusiform structure. During the fifth week of gestation, the dorsal wall of the stomach grows much faster than the ventral wall, resulting in the formation of the greater curvature of the stomach, and deformation of the ventral stomach leads to the formation of the lesser curvature. Continued differential expansion of the stomach leads to the formation of the fundus and cardia by the end of the seventh week. The stomach rotates 90° during the seventh and eighth weeks of gestation around a craniocaudal axis so that the greater curvature lies to the left. At the same time, the right and left vagal plexuses, which originally run through the mesoderm on either side of the gut tube, take up an anterior and posterior position, forming the vagal trunks [32] (Fig. 116.1).

The rotation of the stomach and secondary fusion of the duodenum to the dorsal body wall create the lesser sac of the peritoneal cavity. The final location of the stomach is variable owing in part to its two-point fixation at the gastro-oesophageal junction and gastroduodenal junction, allowing for considerable mobility. The gastro-oesophageal junction generally lies to the left of the tenth thoracic vertebra, with pylorus of the stomach lying on the transpyloric plane, passing through the body of the L1 vertebra.

The stomach is covered in peritoneum except for the 'bare area' at the gastro-oesophageal junction. The peritoneum passes as a double layer from the lesser curvature to the liver as the gastric portion of the lesser omentum and then hangs from the fundus and the greater curvature as the greater omentum, extending to the transverse colon as the gastrocolic ligament, to the spleen as the gastrosplenic ligament and the diaphragm as the gastrophrenic ligament [39] (Fig. 116.2).

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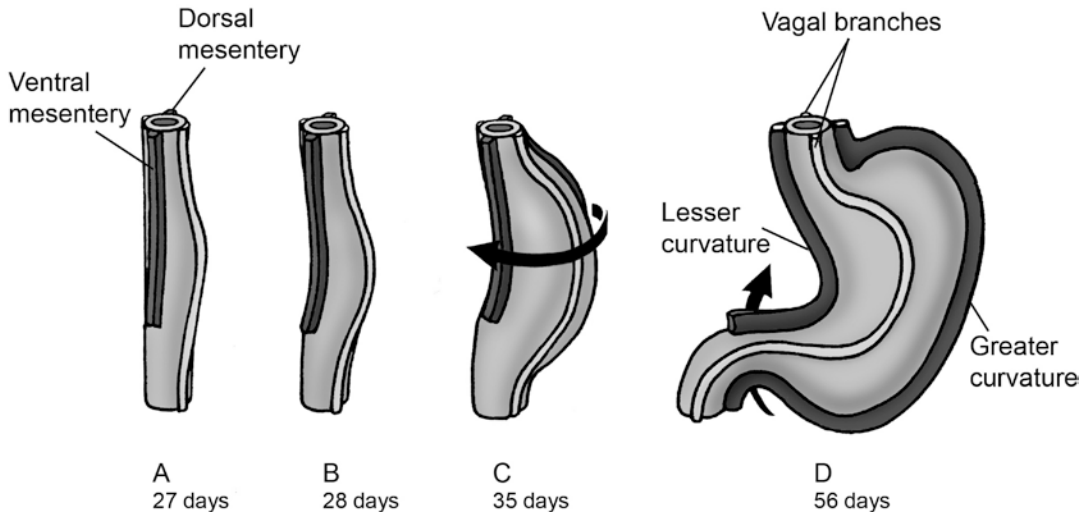

Fig. 116.1 Normal embryological development of the stomach. The posterior wall of the stomach expands during the fourth and fifth weeks to form the greater curvature. During the seventh week (**c**), there is clockwise rotation of the stomach. (**a**–**c** oblique frontal view and **d** direct frontal view)

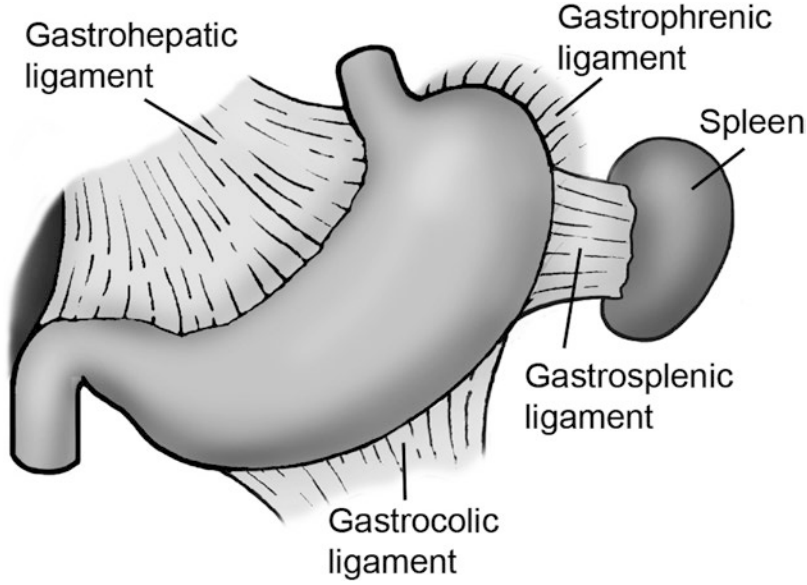

Fig. 116.2 Ligamental attachments of the stomach. Normal ligaments of the stomach include the gastrophrenic, gastrohepatic, gastrocolic and gastrosplenic

The stomach can be divided into five distinct areas, the cardia, fundus, body, antrum and pylorus. The cardia is an ill-defined area near the junction with oesophagus. The fundus is a rounded vault, superior and to the left of the cardia, closely related to the left dome of the diaphragm. The body is the major portion of the stomach, between the fundus and the pyloric antrum. The pyloric part of the stomach is formed from the pyloric antrum (dilated portion) and the pyloric canal (narrow portion). The pylorus itself separates the stomach from the duodenum, the Greek for pylorus being 'gatekeeper'. The stomach has a very rich vascular supply, and

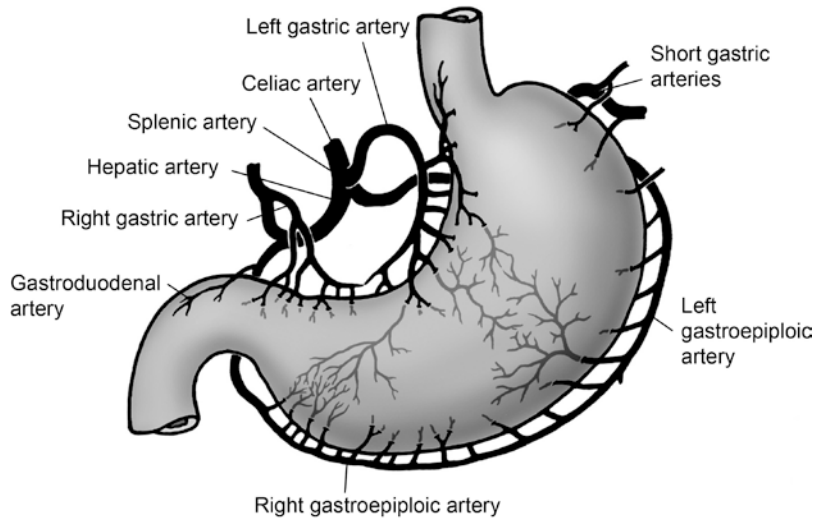

Fig. 116.3 Arterial supply of the stomach

subsequently ischemia of the stomach is very rare. It derives its blood supply from right and left gastric arteries along the lesser curvature, the greater curvature being supplied by the right and left gastroepiploic arteries, together with the short gastric vessels from the spleen. There is also contribution from the posterior branch of the splenic artery and the phrenic arteries (Fig. 116.3).

Venous drainage of the stomach generally accompanies the arterial supply, emptying into the portal vein or tributaries, the splenic or the superior mesenteric veins. Usually the right and left gastric veins drain directly into the portal vein. The right gastroepiploic vein usually drains into the superior mesenteric vein but may enter the portal vein or the splenic vein. The left gastroepiploic vein drains into the splenic vein.

There are four main areas of lymphatic drainage, each of which has its own regional lymph nodes:

1. Lesser curvature drains to the left gastric lymph nodes.
2. Right part of greater curvature drains to the gastroepiploic lymph nodes along the right gastroepiploic vessels.
3. Left part of greater curvature drains into the gastroepiploic lymph nodes along the left gastroepiploic vessels.
4. Lesser curvature of the stomach (related to the pylorus) drains into the right gastric lymph nodes lying along the right gastric artery.

The parasympathetic nerve supply of the stomach is derived from the anterior and posterior vagal trunks and their branches. The sympathetic nerve supply is mainly from the celiac plexus, through the plexuses around the gastric and gastroepiploic arteries. The efferent sympathetic fibres to the stomach arise from T6 to T9 segments of the spinal cord. The anterior vagal trunk usually enters the abdomen as a single branch lying on the anterior surface of the oesophagus. The posterior vagal trunk enters the abdomen on the posterior surface of the oesophagus.

Congenital gastric anomalies are rare. They can have a varied presentation in children, from the neonatal period through to adolescence. The various anomalies in relation to the various anatomical sites in the stomach which are discussed are outlined in Fig. 116.4.

Hypertrophic Pyloric Stenosis (HPS)

HPS is the most common surgical cause of vomiting in infants. It was first described by Hirschsprung in 1888. The pyloric muscle is

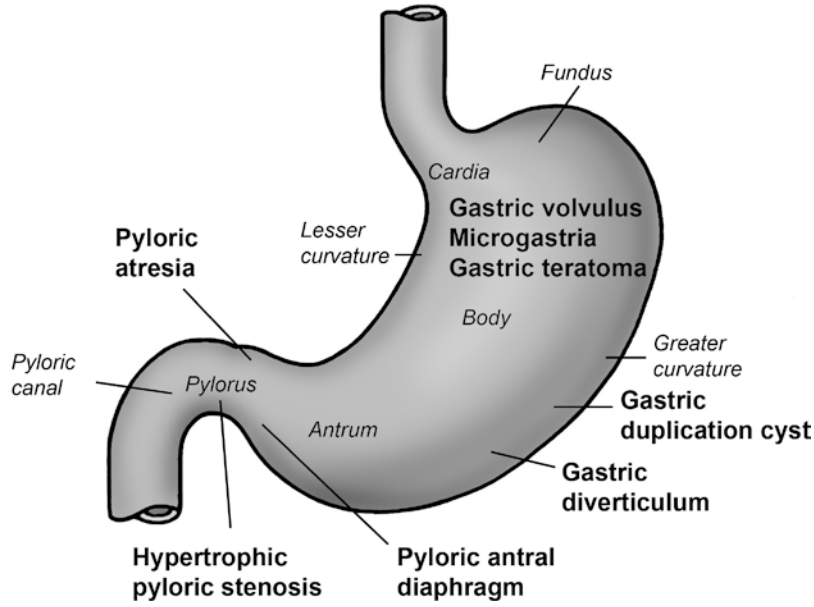

Fig. 116.4 Diagram of stomach showing anatomical areas and the most common sites for congenital anomalies to occur

hypertrophied causing narrowing of the pyloric channel leading to gastric outlet obstruction [50]. The peak incidence of onset is 3–5 weeks of age [48]. It is seen at a rate of 1–4 per 1,000 live births [52, 53, 61, 65]. Males are affected more commonly than female infants at a ratio of 4:1 [23]. Risk factors for HPS include a positive family history, gender, younger maternal age, being the first born infant and maternal feeding patterns [29, 61, 70].

The aetiology of HPS is poorly understood although there have been numerous hypotheses published in the literature including genetic, extrinsic and hormonal factors. Furthermore, abnormalities of various components of the pyloric muscle have been reported including smooth muscle cells, extracellular matrix elements, nerve cells and neurotransmitters. More recently genetic studies have identified susceptible loci for HPS, and molecular studies have concluded that smooth muscle cells are not properly innervated [50].

The classic presentation of HPS is that of non-bilious, projectile vomiting in the full-term infant. Initially the emesis may be infrequent and be mistaken for gastro-oesophageal reflux, but this then progresses to projectile vomiting. On examination, the child may be dehydrated depending on the length of the history, and visible peristaltic waves may be present across the abdomen.

Typically the infant develops a hallmark metabolic derangement of hypokalaemic, hypochloraemic metabolic alkalosis, due to the excessive loss of gastric fluids rich in hydrogen and chloride, and to a lesser extent sodium and potassium. Initially alkaline urine is excreted to compensate for metabolic alkalosis; however as the vomiting and dehydration worsen, maintenance of the extracellular volume through sodium conservation becomes more important, resulting in increased sodium resorption by the renal tubules resulting in potassium loss which is compensated by hydrogen excretion, and a paradoxical aciduria develops, worsening the alkalosis further.

There are various techniques described for palpating the ‘pyloric tumour’ but whichever technique is used requires patience and an optimal examination setting. Ultrasound had become the standard investigation for the diagnosis of pyloric stenosis (Fig. 116.5). The diagnostic criteria for HPS is a muscle thickness of greater

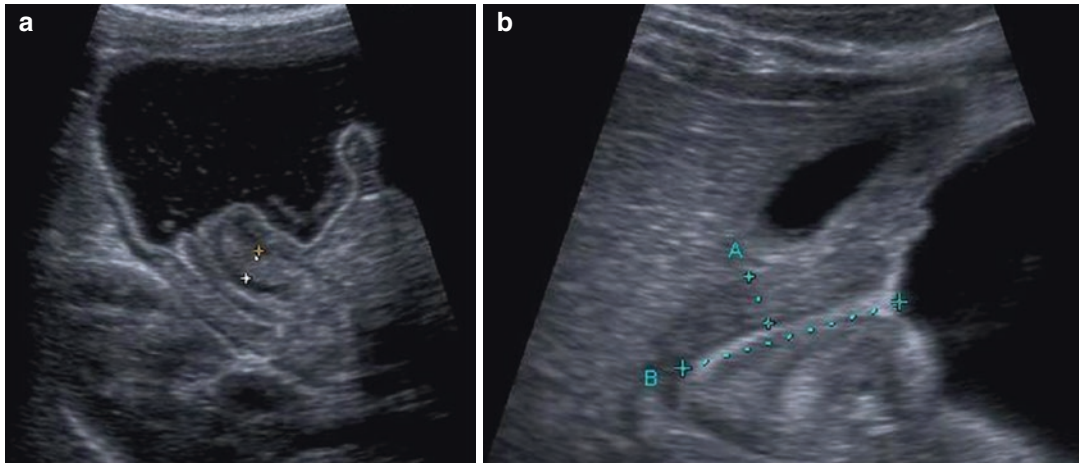

Fig. 116.5 Ultrasound images of hypertrophic pyloric stenosis measuring the width (a) and both diameters (b)

than or equal to 4 mm and a length greater than or equal to 16 mm [29]. In a neonate <30 days, a thickness of 3 mm is diagnostic [31].

The first successful surgical procedure for HPS was performed by Ramstedt in 1912.

Several incisions have been described for the open approach including an incision in the right upper quadrant. A more cosmetic incision is a supraumbilical incision, followed by division of the linea alba or a muscle sparing split of the anterior and posterior rectus sheath, transversely. The pylorus is then delivered through the wound and a longitudinal serosal incision is made, and blunt dissection is used to split the pyloric muscle fibres until the submucosal layer is seen (Fig. 116.6).

The laparoscopic approach is a well-recognised technique, and randomised prospective control trials have not shown any difference in complication rates compared to the open procedure [35, 67]. After establishing the pneumoperitoneum, two further paramedial stab incisions are made in the left and right side of the abdomen for the introduction of the laparoscopic instruments (atraumatic bowel grasper and the pyloromyotomy knife). The pyloric fibres are then incised in a similar method to that described above.

The major postoperative complications of pyloromyotomy include mucosal perforation occurring in 1–2 % of cases [34, 67], incisional

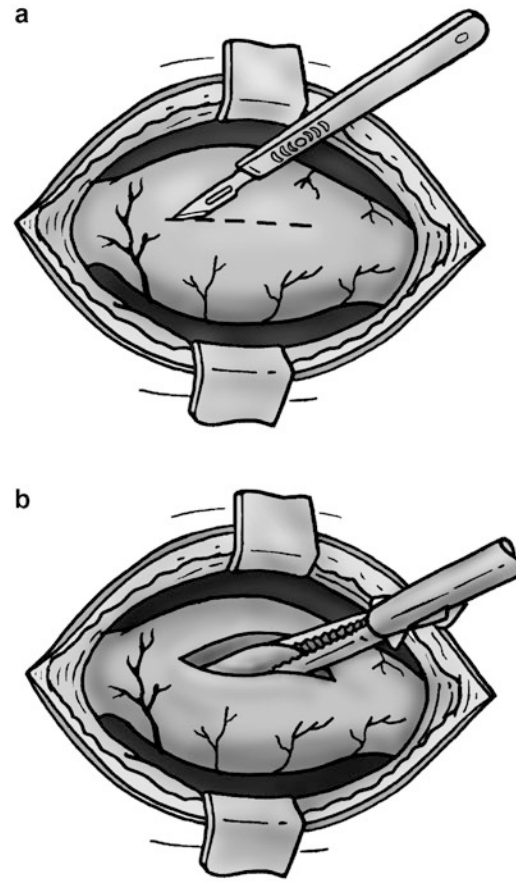

Fig. 116.6 Diagram of open pyloromyotomy. (**a**) The incision is made along the length of the pyloric tumour in the relatively avascular anterosuperior aspect. (**b**) The fibres are slit to expose the bulging mucosa

hernia in 1 % [67], prolonged postoperative emesis and incomplete myotomy. Wound infection occurs in 1–2 % [34, 67]; however there is no evidence to support the use prophylactic antibiotics.

There have been case reports of successful balloon dilatation for HPS in an infant where it was felt that gaining entry to the peritoneal cavity would place the infant at significant risk. Initial reports were unsuccessful, and concerns were raised with regard to the full thickness split of the pylorus. However, Ogawa et al. have reported a successful case in an infant who had previously undergone a staged repair for a giant omphalocele [47]. A pilot, single-centre study of endoscopic pyloromyotomy using a needle knife or standard sphincterotome has been described [24]. Short- to medium-term results showed it to be a safe and effective treatment option in a small cohort of ten infants. However there are no long-term and randomised control trials to support the results for endoscopic pyloromyotomy.

Prepyloric Antral Diaphragm

A prepyloric antral diaphragm is a rare anomaly consisting of a submucosal web of gastric tissue covered by gastric mucosa, found in the distal gastric antrum. Significant associated anomalies (gastrointestinal and cardiovascular) are seen in about 30 % of children with an antral web [6].

In the neonatal period, infants will present with non-bilious vomiting and may have associated respiratory problems and poor weight gain. The diagnosis is made on upper gastrointestinal contrast study in 90 % of patients [6]. The typical appearance of the web is a thin membranous septum projecting into the antral lumen, perpendicular to the longitudinal axis 1–2 cm proximal to the pylorus (Fig. 116.7).

Gastroscopy has been used to accurately identify the pyloric web in older infants and children [68]. Features include:

1. A small fixed central aperture surrounded by gastric mucosa that is smooth and devoid of folds.

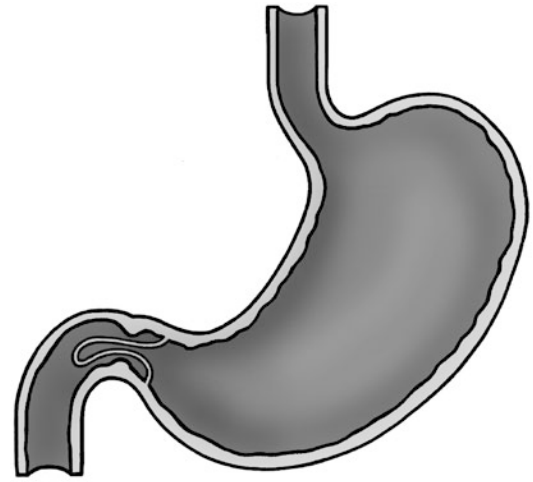

Fig. 116.7 Diagram of prepyloric antral diaphragm

2. No change in the opening size of the web with peristalsis.
3. The gastric wall proximal and distal to the web is seen to contract normally [3].

Surgical correction of the pyloric web involves excision of the web, combined with pyloroplasty as described under the section of ‘pyloric atresia’.

Pyloric Atresia

Pyloric atresia is a rare pathology and constitutes about 1 % of all intestinal atresias. Its incidence is about 1 in 100,000 live births [59], with an equal male/female ratio [25]. It was first described by Calder in 1749 [44, 60], and Touroff et al. presented the first successful operation for the correction of pyloric atresia [44] nearly 200 years later, in 1940.

Pyloric atresia varies from a membranous diaphragm to complete dysfunction at the pyloric level [62] and has three anatomical variants (Fig. 116.8):

1. Type A, pyloric membrane or web occluding the lumen

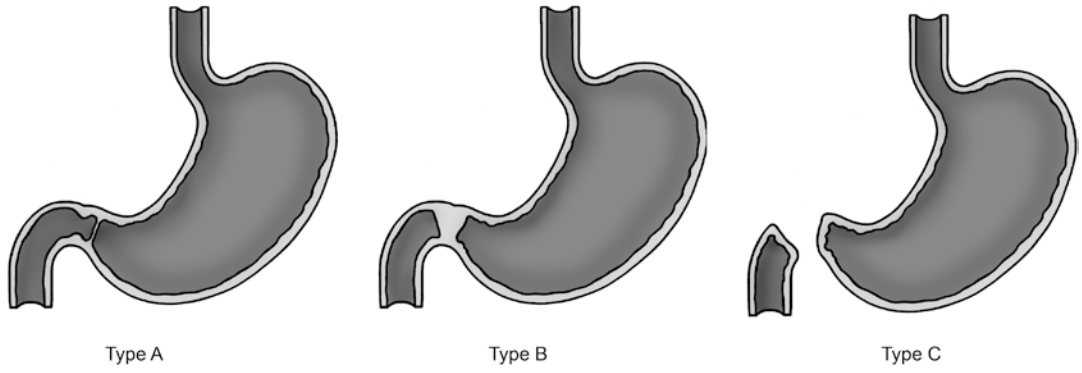

Fig. 116.8 Diagram showing the different types of pyloric atresia

2. Type B, pyloric channel is a solid cord/longitudinal segmental atresia
3. Type C, gap between the stomach and the duodenum/gap atresia [25]

The distribution of anatomical variants in a 15-year review from a single institution was:

- Type A – 57 %
- Type B – 34 %
- Type C – 9 % [25]

The cause of these lesions remains unknown, but embryologically it is thought to result from developmental arrest between the 5th and 12th weeks of gestation. If there is fusion of redundant endoderm before 8 weeks gestation, then discontinuity of gastric wall musculature would result in a segmental defect (type B/C). If the redundancy occurs after 8 weeks gestation, when the muscle layers are complete, then a simple membrane develops (type A) [17].

Congenital pyloric atresia tends to occur as an isolated lesion, which has an excellent prognosis. It is seen in association with other malformations in 30–50 % [15, 19, 27] which can give a negative impact on final outcome. Associated malformations include malrotation, atrial septal defects, vaginal agenesis and tracheo-oesophageal anomalies. Familial occurrence is reported and there is suggestion of autosomal recessive transmission [20, 27]. Eighteen percent of children with pyloric atresia have epidermolysis bullosa (EB) which is a cutaneous genetic disease of variable severity [25]. There are three main types:

1. EB simplex
2. Junctional EB
3. Dystrophic EB

These distinct types are recognised by determining the exact level at which the split responsible for blistering occurs. All three types have been reported to occur with pyloric atresia; however the junctional variant is most common [57, 69]. The distribution of blisters may be localised or generalised and may be present at birth or take up to 48 h to develop after birth. It should be noted that the blistering can affect the gastrointestinal tract, respiratory system and the genitourinary tracts [46]. Evidence suggests that the PA-EB association is a distinct clinical entity and is now referred as the PA-EB syndrome, first described by Swinbourne and Kohler in 1968 [59]. In 1989, Moore [38] reported 125 cases of pyloric atresia and 18 of these were associated with EB [50]. This association is usually fatal within the few months of life, despite surgical correction of the intestinal obstruction [55].

The typical presentation of pyloric atresia is that of non-bilious vomiting, with the absence of generalised abdominal distension (Table 116.1). The epigastrium may be distended if the stomach is large and respiratory problems are not uncommon. Dyspnoea, tachypnoea and excessive salivation may be seen. There may be an antenatal

Table 116.1 Symptoms and sign of pyloric atresia

Symptoms and signs	Occurrence (%)
Non-bilious vomiting	100
Single gastric bubble on radiograph	98
Passage of meconium	69
Polyhydramnios	63

Data from Muller et al. [42] and Lorenzet and Morger [35]

history of polyhydramnios. A delay in diagnosis can lead to severe metabolic acidosis and dehydration, and if the gastric distension is gross, gastric perforation can result.

Abdominal radiographs characteristically show a single gas bubble representing the distended stomach, with no distal gas (Fig. 116.9). Upper gastrointestinal studies although often unnecessary show complete obstruction of the stomach generally at the level of the antrum or pylorus.

Following adequate resuscitation and correction of electrolyte disturbance and protein losses (exacerbated by EB), the surgical treatment of pyloric atresia varies depending on the type of atresia. The options available include:

- Type A: Excision of pyloric web in combination with pyloroplasty
- Type B: Finney or Heineke-Mikulicz pyloroplasty if the solid pyloric atresia is short
- Type C: Excision of the atretic segment and gastroduodenostomy [4, 19, 46, 56]

After identifying the pylorus, a longitudinal incision is made from the gastric side of the pylorus to the duodenum (length 1.5–2 cm) midway between the greater and lesser curvatures of the stomach. The membrane is then excised circumferentially and the mucosa is approximated. After establishing patency of the remaining bowel, the longitudinal incision is closed transversely in two layers [55].

Congenital Microgastria

Congenital microgastria is a rare anomaly. Its clinical manifestation depends on the stage at which embryological development of the stomach is arrested during the fifth week, when differentiation of the greater curvature occurs; neither rotation nor fusiform dilatation of the stomach occurs [17]. In most cases the stomach is represented by a small, saccular or tubular structure with minimal reservoir capacity and is often associated with a megaoesophagus. This anatomical finding leads to postprandial vomiting, gastro-oesophageal reflux and malnutrition [71].

It is frequently associated with other congenital defects including the VACTERL association [22], asplenia (embryologically the spleen is derived from the dorsal mesogastrium which has an intimate relation with the developing stomach), intestinal malrotation and duodenal atresia and renal, limb, central nervous system and cardiopulmonary malformations [71]. It has been suggested that microgastria with limb defects, including radial, ulnar and thenar hypoplasia, and central nervous system anomalies [27, 36, 64] has a genetic basis with an autosomal recessive pattern of inheritance [26].

The clinical presentation is typically of an infant with postprandial vomiting and malnutrition. Diarrhoea due to rapid gastric emptying may also be apparent. The diagnosis of microgastria is easily made with upper gastrointestinal studies showing a small tubular or saccular midline structure which is frequently associated with an incompetent lower oesophageal sphincter and as mentioned, in some cases, a dilated oesophagus.

Before the description of gastric augmentation, congenital microgastria was managed conservatively with generally poor outcome including reduced somatic growth, sexual underdevelopment, delays in cognitive milestones and dumping syndrome [2, 7, 21, 28], although positive outcomes have been reported in less severe forms [2].

The creation of a food reservoir (Hunt-Lawrence pouch) was initially described as a procedure to restore continuity of the bowel in patients who had undergone total gastrectomy for gastric cancer [23, 33]. Its use as a gastric augmentation in children with microgastria was first described by Neifeld et al. in 1980 [45]. This procedure, as originally described, includes a

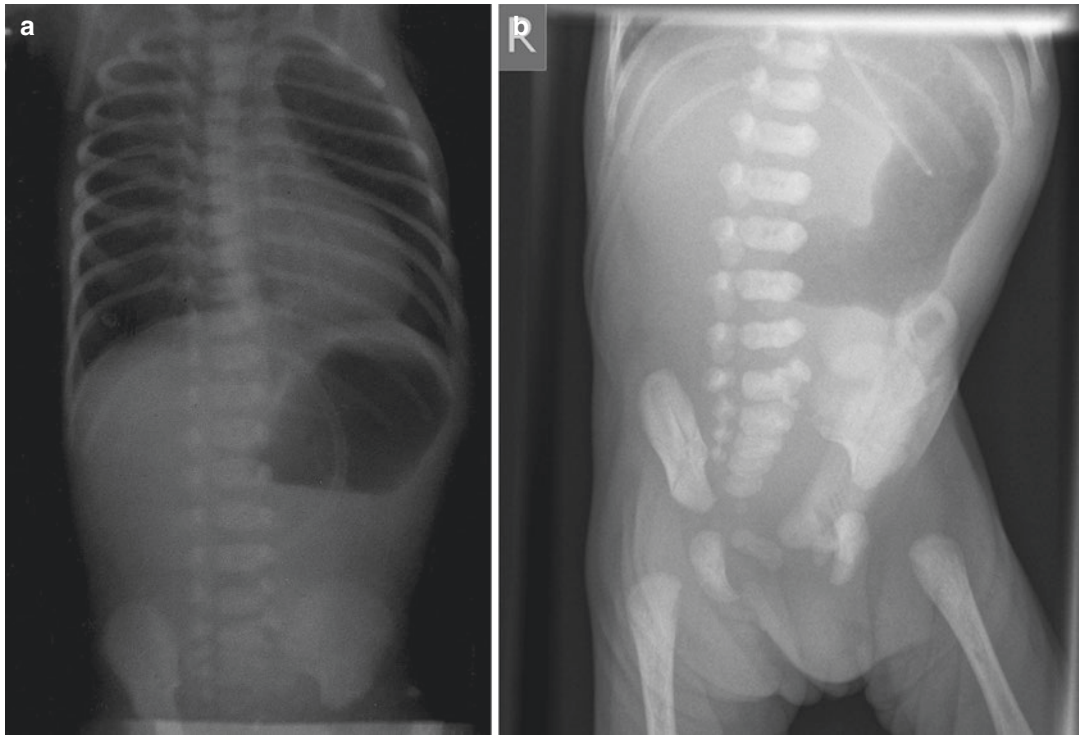

Fig. 116.9 Plain abdominal radiographs showing distended gastric bubble in pyloric atresia

Roux-en-Y from a proximal loop of jejunum to prevent alkaline reflux and a food pouch made by anastomosing, in a side to side fashion, a proportion of the distal jejunal segment (Fig. 116.10). This procedure provides an adequate pouch for food intake and lessens the requirements for frequent feeding. It also facilitates drainage of duodenal contents, decreasing the incidence of alkaline reflux oesophagitis [71].

Postoperatively the patient requires careful follow-up and the regular administration of vitamin B12, and naturally those with asplenia need appropriate penicillin prophylaxis and vaccinations [41].

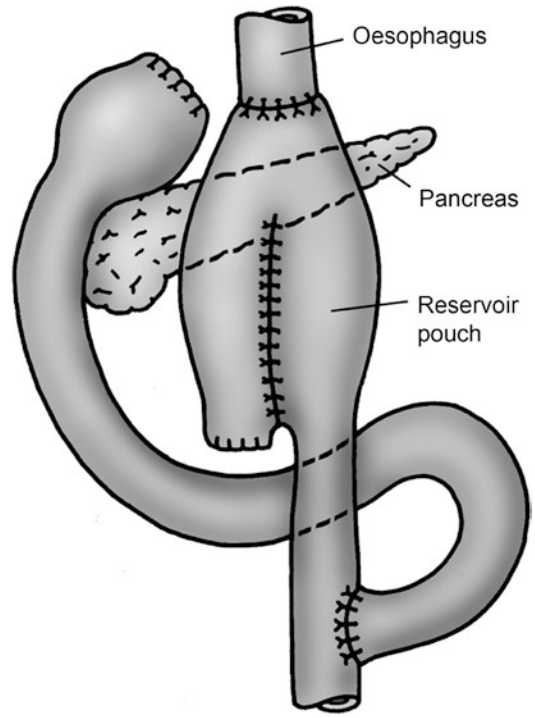

Fig. 116.10 Diagram of Hunt-Lawrence pouch

Gastric Duplication Cyst

Duplications of the stomach are extremely rare and represent 3.8 % of all duplications of the gastrointestinal tract [30, 54]. Most (80 %) are diagnosed in infancy and may be seen on antenatal scans and 65 % occur in females [17]. The majority of gastric duplications tend to occur along the

greater curvature [22] or the posterior wall of the stomach and contain all layers of the gastric wall. They do not usually communicate with the gastric lumen and tend to form a tubular, fusiform or spherical cystic mass [17]. Occasionally there may be a connection to other organs and these can be congenital or acquired. Acquired fistulae can develop due to peptic ulceration, and there are reports of communication to the lung, colon, umbilicus, Meckel's diverticulum [5, 66] and pancreas [40].

Common clinical features include failure to thrive, gastro-oesophageal reflux, abdominal swelling, vomiting and a palpable mass. The cysts may rupture producing peritonitis or may be associated with peptic ulceration and haemorrhage. Fifty percent of patients will have associated anomalies including duplication of the oesophagus and vertebral anomalies [72], and there are published case reports of patients being diagnosed in adulthood with associated pancreatic duct abnormalities [9, 43].

Gastric duplications can be excised by a limited gastrectomy, but on occasions a more extensive resection may be required. There have been reports of creating a window in a dividing septum to form a common lumen; however this is considered to be inferior to excisional surgery. With associated pancreatic duct abnormalities, care must be taken not to injure normal pancreas, and it may be necessary to resect an accessory pancreas [22].

Gastric Diverticulum

Gastrointestinal diverticulae are rare and can occur anywhere along the gastrointestinal tract. Gastric diverticulae have been observed in 0.03–0.1 % of upper gastrointestinal contrast studies and 0.3 % of post-mortem examinations [49, 63]. They can be found at all ages but typically present in the second to fourth decade of life. Seventy-five percent are found on the posterior stomach wall. The majority are congenital (70 %) [58] and solitary, consisting of all layers of the stomach wall. The remaining diverticulae are seen at the pylorus and antrum of the stomach. The finding of ectopic pancreatic tissue suggests a congenital origin, but the majority diagnosed are acquired and secondary to peptic ulcer disease and malignancy, for example [12].

The clinical signs and symptoms of a gastric diverticulum depend on the location, size and presence of ectopic pancreatic tissue. Common presenting features are vomiting, abdominal pain, weight loss, fatigue and anaemia. More serious complications include obstruction, gastro-oesophageal reflux and perforation.

The diagnosis of a gastric diverticulum can be made on endoscopy and upper gastrointestinal contrast studies. The diverticulum appears as a well-circumscribed, smooth, rounded projection from the gastric lumen. The patient must be repositioned in all directions to increase the diagnostic yield of the contrast study. If the lumen of the diverticulum is very narrow, contrast may not enter diverticulum, resulting in the lesion being missed.

In the case of an incidental finding of gastric diverticulum, treatment may not be necessary. If symptoms are thought to be secondary to the diverticulum, then the lesion may be invaginated or amputated. There is a risk of malignancy associated with distal diverticulae and resection has therefore been recommended [17].

Gastric Teratoma

Gastric teratomas are rare benign lesions that occur almost exclusively in males [17]. They account for 1 % of all teratomas [18]. These tumours may have their origins in pluripotent cells and contain all three embryonic germ cell layers. The tumours are often large and multicystic usually on the lesser curvature or posterior wall of the stomach, but the whole stomach may be involved [17].

Clinically the tumours present with haematemesis or non-bilious vomiting due to gastric outlet obstruction with the mean age being 3 months. Antenatal polyhydramnios may be apparent due to gastric obstruction.

Radiographic examination may show calcification and USS may demonstrate solid and cystic

areas within the mass. Upper gastrointestinal studies often delineate the relationship of the tumour to the stomach, but CT/MRI is used to evaluate regional infiltration.

Tumour excision with primary gastric repair is the preferred treatment and is curative. Partial or total gastrectomy is required for intramural tumour extension. Malignant transformation to adenocarcinoma has been reported [8].

Gastric Volvulus

Gastric volvulus is rare but is an important differential diagnosis in those presenting with features suggestive of gastric outlet obstruction. Volvulus results in progressive distension of the stomach with air and fluid which aggravates the obstruction and eventually leads to ischemic necrosis and perforation [14].

The normal stomach is prevented from twisting by its mesenteric attachments (gastrocolic, gastrosplenic, gastrohepatic and gastrophrenic ligaments) as shown in Fig. 116.2. Two further points of fixation include the peritoneal fixation of the pylorus and the cardia. Together these structures anchor the stomach in position and help to prevent excessive movement. Degrees of ligamentous laxity, agenesis and disruption, together with over distension of the stomach and diaphragmatic herniation of the stomach, can lead to abnormal rotation of one part of the stomach around another, resulting in gastric volvulus with complete gastric outlet obstruction.

Gastric volvulus is classified according to the axis around which the stomach rotates (Fig. 116.11). The stomach may rotate on a longitudinal axis that extends from the gastro-oesophageal junction to the pylorus, and this is termed 'organoaxial' volvulus and occurs in two-thirds of patients. Rotation about this axis results in the greater curvature of the stomach resting superiorly to the lesser curvature, giving the suggestion of an upside-down stomach.

The other axis around which the stomach may rotate is around an imaginary line passing from the greater curvature to the lesser curvature. This form is known as 'mesenteroaxial' volvulus. Here the stomach tends to lie in a more vertical plane with the antrum and pylorus rotated anterior and superior to the gastro-oesophageal junction. Also recognised is a 'combined' type of volvulus which is a combination of organoaxial and mesenteroaxial volvulus.

In 1904, Borchadt described a triad of features that were present in an adult who died of acute gastric volvulus and necrosis. These were:

1. Inability to vomit (retching)
2. Severe epigastric distension
3. Inability to pass a nasogastric tube

It has been recognised that these features are not always present in the paediatric population and only 70% of patients have all three symptoms. Other features include chest pain, dysphagia, dyspnoea, dyspepsia and borborygmi [37]. The clinical symptoms often depend on the extent or degree of rotation and obstruction [11].

Symptoms in the paediatric population can range from a chronic history of non-specific abdominal pain to a major intraabdominal catastrophe. Children with neurological impairment have numerous causes for retching and this may lead to difficulty in making the correct diagnosis.

A distended stomach in an abnormal position should raise the suspicion of gastric volvulus, and a single radiograph is usually diagnostic [16]. In contrast to the clinical presentation, the radiological features of gastric volvulus are usually characteristic. The primary radiological sign is viscus containing air. The concomitant pyloric obstruction results in a massively dilated stomach and usually paucity of gas within the remainder of the gastrointestinal tract. On a plain radiograph, any associated diaphragmatic anomalies will also be seen.

Acute mesenteroaxial volvulus can be diagnosed on an abdominal radiograph by identifying the pylorus/antrum being higher than gastro-oesophageal junction, with a distended stomach appearing spherical in supine radiographs. In erect radiographs, there is a double air fluid level seen; one bubble in the fundus and one in antrum. It is important to perform the

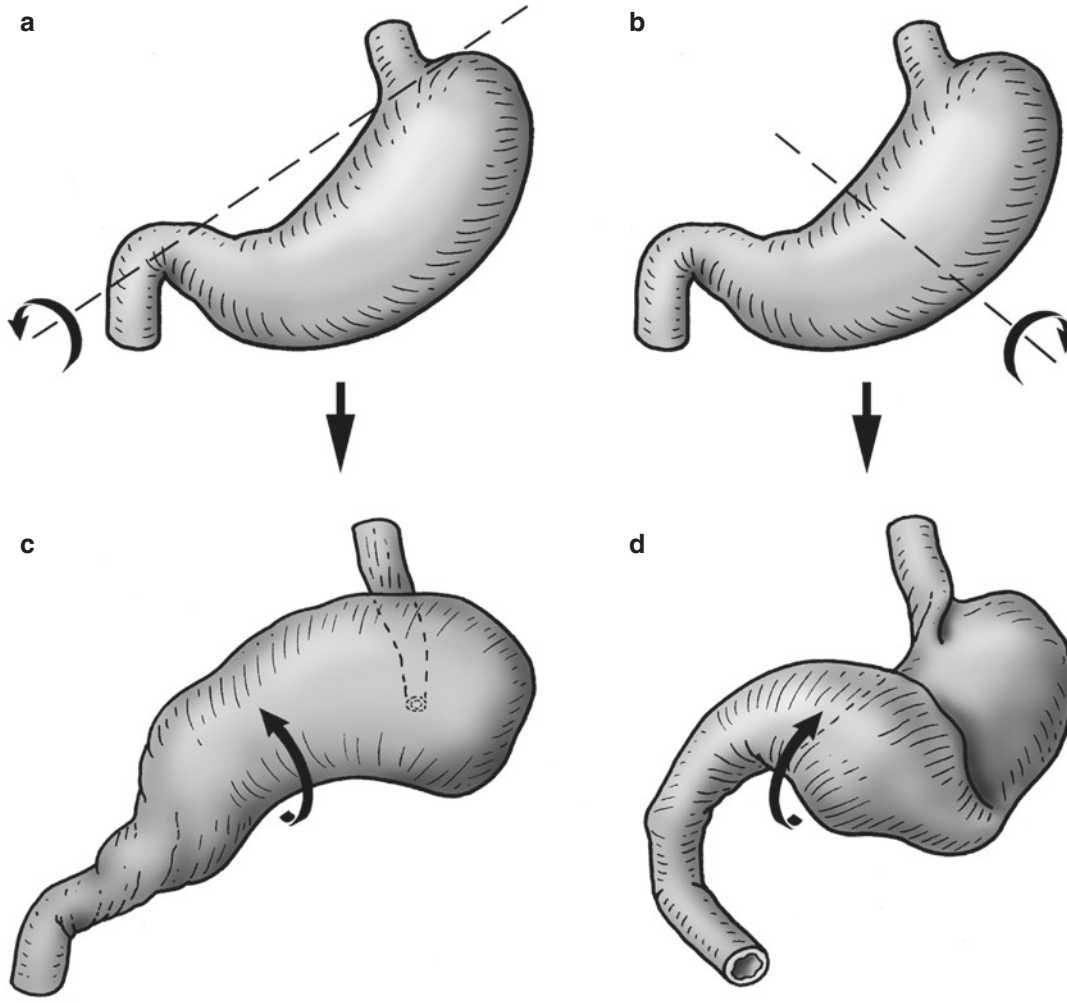

Fig. 116.11 Gastric volvulus. (**a**) Organoaxial axis. (**b**) Mesenteroaxial axis. (**c**) Organoaxial volvulus and 'upside-down stomach'. (**d**) Mesenteroaxial volvulus

radiographs in the erect and supine positions because the extent of rotation is less significant in chronic gastric volvulus than in acute gastric volvulus.

In the organoaxial type, the stomach lies rather horizontally on the plain film with a single fluid level. In organoaxial volvulus, the body of the stomach is inverted, and the greater curvature lies at a higher level than the lesser curvature with the pyloric canal crossing the distal oesophagus. The pylorus usually points downwards and is often near the level of the gastro-oesophageal junction. A single long air fluid level is usually noted on the erect plain film when the volvulus is complete.

Barium examination shows the stomach upside down and documents the obstruction in mesenteroaxial volvulus, while in organoaxial volvulus the gastro-oesophageal junction appears lower than normal and the antrum and pylorus are distended. These radiological findings are virtually diagnostic of gastric volvulus. Endoscopy has been reported as being useful in the diagnosis of intermittent gastric volvulus. Intraoperative gastroscopy demonstrates spontaneous organoaxial volvulus only when the stomach is distended with air [10].

The treatment of gastric volvulus is variable depending on the type. Acute gastric volvulus requires emergency surgery. Chronic gastric volvulus, on the other hand, can be treated conservatively, unless symptoms are severe [1]. Effective treatment for acute gastric volvulus in children requires immediate surgical intervention after appropriate resuscitation. Initially gastric decompression may be required to facilitate reduction of the stomach and prevent impending gastric ischemia [37]. In adults, a nasogastric tube is routinely used; however there are risks of perforation in children; therefore, intraoperative decompression may be required and a gastrostomy serves this purpose well. Earlier reports have advocated the use of trocar decompression, but mortality (33 %) curtailed its use [13]. Endoscopic decompression has also been used in adults but again, perforation risks are high in the paediatric population [51]. Mechanically, only three points of fixation are required to prevent twisting or turning, and the treatment of gastric volvulus works on this simple principle [68].

Surgical correction should include reduction, primary repair of associated anatomical defects and fixation of the stomach. An abdominal approach is recommended even in the presence of an intrathoracic stomach to ensure identification of all associated anatomical defects and to facilitate reduction of the dilated stomach. Gastric fixation is required to prevent recurrence. There have been reports of patients with simple reduction having a recurrence of gastric volvulus [37]. Miller et al. [37] in their review reported no recurrence in children who had undergone gastrostomy fixation. However Cribbs et al. [72] in their review of the literature found nine acute cases in children with a previous history of gastric surgery.

Chronic gastric volvulus is being diagnosed with increased frequency, and this is thought to be due to the increasing use of barium in the evaluation of infants with repeated episodes of vomiting and chest infections. The treatment for chronic gastric volvulus should depend on the severity of the symptoms. Those with mild to moderate symptoms should be treated conservatively [1].

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Congenital Pyloric Stenosis, Webs and Strictures

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H. Till

Congenital gastric outlet anomalies (CGOA) are extremely rare and represent only about 1 % of all gastrointestinal atresias [1]. Embryologically, these malformations are most likely caused by a developmental disturbance of the distal foregut, which forms the antrum and the first, supraampullary portion of the duodenum [2]. In pathological nomenclature, the term represents several different entities like congenital pyloric atresia (CPA), a congenital pyloric stenosis (not to be interchanged with a hypertrophic pyloric stenosis) and intraluminal mucosal webs with or without a central hole (windsock anomaly) [2]. Even a non-folded stenotic ring separating two gastric chambers has been described [3]. Associated anomalies are common [4]. Especially hereditary multiple intestinal atresias (HMIA) are of major clinical importance [5], because these patients often suffer from severe forms of immunodeficiency [5, 6]. Today it remains unclear, whether such immunological defects occur primarily or secondary to the intestinal dysfunction [4]. Finally, an association of the CPA with an epidermolysis hereditaria bullosa (EHB) [2, 7] is well known.

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The first suspicion of a gastric outlet obstruction is raised during prenatal ultrasound investigations. Detection of polyhydramnion, presence of an extremely distended stomach or absence of intestinal filling and motility offer clues towards an impaired gastrointestinal (GI) passage in the foetus. Postnatally the clinical symptoms vary considerably in terms of onset, severity (acute versus chronic), tolerance of feedings and vomiting. A neonate with a complete obstruction (e.g. due to a CPA) usually presents with low birth weight, a small abdominal cavity and non-bilious vomiting. Older children (e.g. those with gastric webs) may complain about chronic and unspecific abdominal pain for some time, non-bilious vomiting and failure to thrive.

Most CGOA can be diagnosed by an upper GI study and an endoscopy. Plain abdominal films possibly demonstrate a “single bubble” and the absence of gas in the distal gut. Even webs, membranes and windsock deformities should be detected on fluoroscopic investigations. Endoscopy has an added advantage that it not only confirms the diagnosis but also enables the possibility for immediate treatment by laser coagulation or sharp dissection of webs. Recently Lin et al. [3] reported about their experience with congenital outlet obstructions of the GI tract. In 37 cases they found 12 gastric, 22 duodenal and 3 jejunal obstructions. Ten of the 12 gastric anomalies underwent an

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endoscopy and a detection of the lesion was possible in every case. Three of these anomalies were webs and could be resected concomitantly. The remaining nine gastric obstructions comprised of non-folded rings or atresias, which were resected. Al-Sahem [1] published a similar experience with 11 cases of gastric outlet obstructions. Intraoperatively, five had a pyloric diaphragm, three had a CPA with a gap between the two segments and two had a CPA without a gap. The pyloric diaphragms were excised during a Heineke-Mikulicz pyloroplasty. The CPAs received a gastroduodenostomy. Although most of his patients did well after the procedures, there was a late 45 % mortality due to sepsis that resulted from an associated immune deficiency.

In summary, children with isolated gastric outlet obstructions have a good prognosis. Prompt endoscopic confirmation and surgical treatment are recommended. However, the associations of EHB or HMIA imply a high mortality due to sepsis and severe immunodeficiencies. These patients require a multimodal therapy beyond surgery.

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Gastric Volvulus

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Introduction

Gastric volvulus (GV) is a rare cause of partial or total foregut obstruction in paediatric age. This potentially life-threatening condition is characterised by a twisting of the stomach more than 180° on its longitudinal or transversal axis with probable gastric ischemia and perforation. If the rotation is less than 180°, a gastric torsion is present. Delay in diagnosis can result in a high rate of morbidity and mortality.

Historical Background

The term "volvulus" derives from Latin "volvere", which means to turn or roll. Historically, the first reference to a GV dates back to Ambrose Paré (1579) who talked about a complete twist of the stomach due to a sword injury in the left diaphragm. In 1866, Berti anatomically described a case of acute GV based on an autopsy of a 61-year-old woman [6]. In 1895, Berg performed the first surgical procedure to resolve a GV in a 41-year-old man; he reduced the bulky gastric distension using a trocar before derotating the stomach; 12 days after, the patient was discharged in good health conditions [5]. In 1904, Borchardt reported the triad of symptoms and signs of GV: severe epigastric pain, retching without vomiting and failure to pass a nasogastric tube [7]. In 1899, Oltmann illustrated the first paediatric case of GV, and, until 2008, there have been less than 600 reported cases of GV in children [9].

Epidemiology

GV in infants, children and adolescents is a rare pathological condition. Cribbs and colleagues identified 581 paediatric cases of GV published in the English literature between 1929 and 2007. Of these cases, 252 children (43 %) had an acute onset, of which 136 (54 %) with organoaxial volvulus, 103 (41 %) with mesenteroaxial volvulus, 5 (2 %) with combined volvulus and 8 (3 %) with not characterised volvulus [9]. A minimal predominance in male patients was observed [18]. The acute form of GV is frequently described in the first year of life, generally associated to congenital diaphragmatic abnormalities and intestinal malrotation. In older paediatric patients, other predisposing factors are identified, such as paraoesophageal hernia, hiatal hernia, wandering spleen or asplenism. In untreated acute GV, the mortality rate is more than 80 % [13], while in

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patients promptly operated the prognosis significantly improves (mortality: 6.7 %) [9].

Classification

GV may be classified according to its causes and axis of rotation. Depending on aetiology, GV is recognised as idiopathic or acquired. The primary or idiopathic subtype is less common (35 %) [17], and it occurs as a result of hyperlaxity, elongation or absence in the attachments of the stomach that is normally held in place by the oesophageal hiatus, retroperitoneal fixation of duodenum, short gastric vessels and four ligaments: the gastrocolic, gastrohepatic, gastrophrenic and gastrosplenic. Together these structures anchor the stomach and prevent malrotation. The secondary GV is more common (65 %) [17], and it may be related to disorders of gastric anatomy (peptic ulcer, tumours) or function (gastric hypomotility, acute or chronic distension typical in children with neurological impairment), abnormalities of adjacent organs such as the diaphragm (eventration, hiatal or paraoesophageal hernia, congenital diaphragmatic hernia, phrenic nerve palsy) (Fig. 118.1a, b) or spleen (asplenism, wandering spleen) [23] and foregut malrotation. Previous abdominal surgery with interruption of gastric ligaments, as in liver transplantation [12] and fundoplication, can predispose to volvulus. In 1940 Singleton [27] identified three types of GV according to the axis of rotation:

1. Organoaxial GV (Fig. 118.2): the stomach rolls around the longitudinal axis, extending from the gastro-oesophageal junction to the pylorus. The antrum rotates in opposite direction to the fundus of the stomach. It is the most common entity usually associated to diaphragmatic defects, wandering spleen, asplenic or polysplenic syndrome. Recurrently this form manifests as an acute event [19].
2. Mesenterico-axial GV (Fig. 118.3): the stomach twists around a horizontal axis passing through the greater and lesser curvatures. The antrum rolls superiorly and anteriorly and the posterior surface of the stomach lies anteriorly. Generally this is an idiopathic condition with chronic or intermittent symptoms [19].
3. Mixed GV: it is an extremely rare entity due to the combination of organoaxial and mesenterico-axial types.

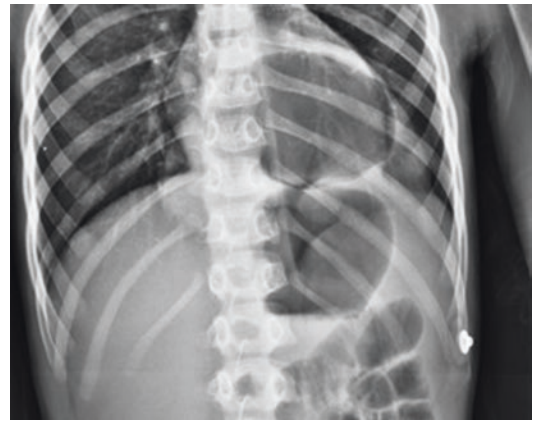

Fig. 118.1 Radiological finding of paraoesophageal hernia after Nissen fundoplication (frontal view)

Clinical Presentation

The onset of GV varies depending on aetiology and degree of the rotation of the stomach and resulting obstruction. In the acute form, the triad of Borchardt (severe epigastric distension, intractable retching and inability to pass a nasogastric tube) is diagnostic in 70 % of adult patients, whereas in the majority of children is usually absent or incomplete. In paediatric population severe symptoms could include most frequently vomiting, dysphagia, dyspepsia and, in case of diaphragmatic defect with cardiopulmonary impairment, chest pain and acute respiratory distress. Hematemesis may also be present, due to mucosal sloughing as a result of ischemia or a mucosal tear for retching. The secondary complications of acute GV consist of gastric ileus, pyloric ischemia and subsequent gastric outlet obstruction, gastric necrosis with perforation and even death. In idiopathic volvulus, the upper abdomen may be distended and severe pain localised in epigastric region; in secondary GV, when related to diaphragmatic anomalies, the abdomen

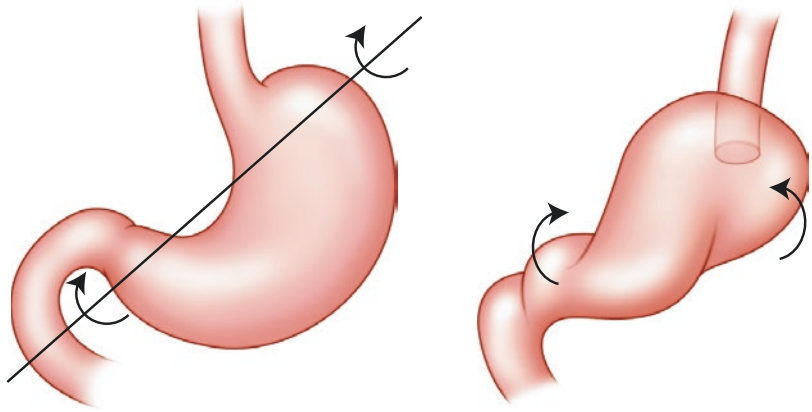

Fig. 118.2 Organoaxial volvulus: the stomach rolls around its longitudinal axis

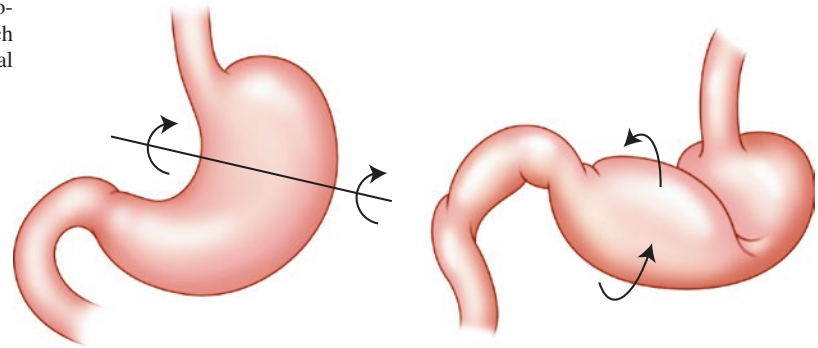

Fig. 118.3 Mesentericoaxial volvulus: the stomach twists around its horizontal axis

may be soft and flat, whereas anomalies could be detected in chest. Patients affected by chronic GV may present mild and non-specific symptoms such as intermittent epigastric pain, early satiety, nausea, recurrent vomiting, sporadic dysphagia, irritability and failure to thrive. These clinical manifestations could appear irregularly for weeks to years and may go underdiagnosed [17]. It must be emphasised that there is a high probability for the chronic form to become acute [13].

Diagnosis

The recognition of GV is often difficult and non-specific. Radiological investigations play an important role in diagnosis and especially in surgical strategies. Traditional X-ray exam is significant to detect gastric dilatation with scarcity of gas in the remaining part of foregut; if GV is secondary to a diaphragmatic defect, retrocardiac air bubble or air-fluid level can be found in the chest. Particularly, in mesenterico-axial form the gastric shadow shows double air-fluid levels in an erect position, whereas in the organoaxial one the stomach is positioned more horizontally with a single fluid level. On the other side, upper gastrointestinal series (UGIS) is considered more specific than traditional X-ray; UGIS reveals obstruction of the stomach at the site of volvulus and its distension at the level of the diaphragm, lying in a horizontal (organoaxial volvulus) or vertical (mesenteroaxial volvulus) plane. Computed tomography scan (CTS) confirms the diagnosis with anatomical details and ascertains possible associated conditions (paraoesophageal or hiatal or congenital diaphragmatic hernias, diaphragmatic eventration) [1, 20, 22, 29, 30].

Treatment

To ensure a good outcome for patients with GV and to reduce the rate of complications and mortality, early diagnosis is required. The treatment can be conservative or surgical: it depends on

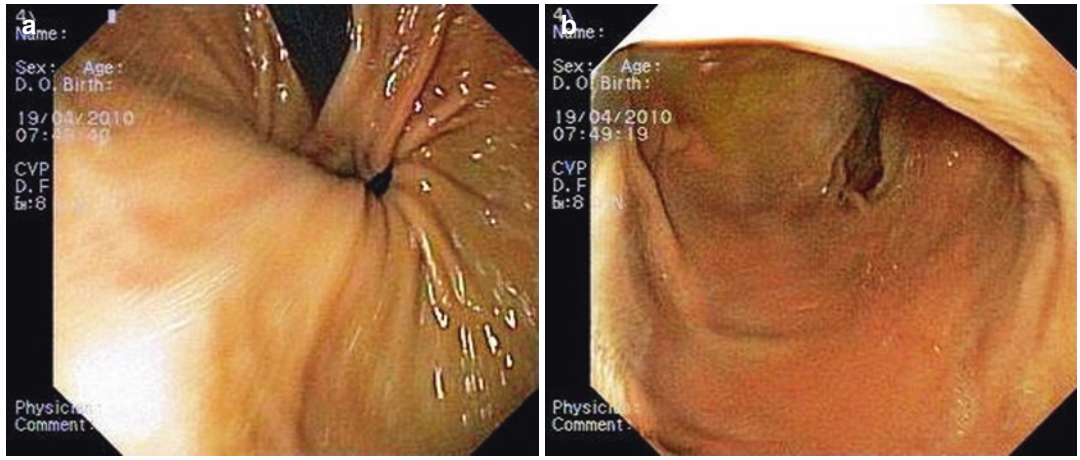

Fig. 118.4 (**a**) Endoscopical view: giant paraoesophageal hernia. (**b**) Endoscopical view: paraoesophageal cavity

the acute or chronic clinical presentation and on potential connected anomalies. Whereas the acute onset must be treated with an emergent surgical intervention, there are no clear guidelines about the management of the chronic one.

Acute GV

In case of acute symptoms, the surgical approach consists of decompression, derotation, fixation of the stomach and handling of associated anomalies. In paediatric age, gastric decompression with a nasogastric tube or with endoscopy is controversial for known risk of perforation [11]. An alternative approach is a trocar placement or an intraoperative decompression with a gastrostomy tube. After gastric derotation, a fixation of the stomach is advised to prevent recurrence [14]. Darani and colleagues proposed a triple gastropexy: anterior gastropexy, phrenofundopexy and esophagocardiopexy. The latter is performed to avoid the opening of His angle, which is due to the two previous steps of the treatment and could favour gastro-oesophageal reflux disease (GERD) [10]. On the contrary, some authors fixed the stomach only with a gastrostomy [16], but cases of recurrent volvulus were reported with a torsion of the stomach around an axis extending from the gastro-oesophageal junction to the gastrostomy site [3]. For this reason, Mayo and colleagues add an anterior gastropexy to a Stamm gastrostomy in all patients treated [17]. A combined laparoscopic and endoscopic approach to create an anterior gastropexy has been reported in children with intermittent primary gastric volvulus. With the gastroscope in place and under laparoscopic guidance, it is possible to fix the stomach at the abdominal wall with percutaneous sutures and in nonrotated position [8]. Fundoplication is often advocated by some surgeons who attribute the increased incidence of reflux to dissection and mobilisation of lower sphincter [4] or to anomaly of diaphragmatic hiatus or to gastropexy. In presence of localised gastric necrosis, limited resection can be performed in order to maintain gastric continuity; if a complete necrosis is found, a gastrectomy could be necessary [15]. In secondary acute GV, the treatment aims to cure any predisposing factors (diaphragmatic defects, intestinal malrotations, wandering spleen, asplenism, paraoesophageal hernia and large hiatal hernia). The large paraoesophageal hernia (Fig. 118.4a, b) could be repaired with a mesh or with direct crural closure depending on the width of the diaphragmatic hiatus. In case of wandering spleen, splenopexy with a mesh or natural tissue or with the placement of the spleen in a "pouch" and associated gastropexy are recommended [28]. When the GV is originated by a diaphragmatic hernia, it could be useful to decompress the stomach before derotating it. With growing use of

laparoscopy, several authors prefer this minimally invasive technique to resolve GV [24]. Bawahab et al. developed an algorithm to define when the laparoscopic method should be attempted. After the first procedures to resuscitate the patient and decompress the stomach with a nasogastric tube, the clinical status must be evaluated; if the patient conditions are unstable and a gastric leak or gastric ischemia is, respectively, documented with a UGIS or an endoscopical exam, urgent open surgery is indicated. If patient's clinical conditions are stable, the contrast study reveals good flow of contrast into the stomach or gastroscopy visualises a normal gastric mucosa, a laparoscopic operation could be performed. This algorithm, used for adult patients with GV by giant paraoesophageal hernia, is useful to avoid emergent surgery and plan the operation in laparoscopy by a surgeon with advanced laparoscopic expertise [4]. To decrease intraoperative complications, Palanivelu et al. advise to maintain a pneumoperitoneum pressure between 10 and 12 mmHg to ease the reduction of hernial contents, if the procedure is performed laparoscopically; to avoid traction on the stomach to prevent serosal lesions; to divide the sac from the pleura carefully to keep away from pneumothorax; and to pay attention when dissecting the right crus, as the left gastric vessel may herniate with the stomach across the edge of the crus [21]. Trocars must be placed high on the abdominal wall to allow instruments to reach into the chest.

Chronic GV

The intermittent chronic neonatal GV is a specific entity, which should be an asymptomatic or poor symptomatic form caused by lax ligamentous attachments because of maternal hormones. Generally this condition is suggestive of an organoaxial partial volvulus, called "floppy stomach", with a spontaneous resolution, diagnosed occasionally during a UGIS performed for other diseases [25]. When the chronic GV is characterised by mild to moderate symptoms, the conservative management should be effective. This onset is typical in children with neurological impairment and is related to a chronic gastric distension due to aerophagia [31]. In these cases, patient undergoes gastric decompression and is maintained in the prone position with slight head up rather than the supine position. Al Salem AH proposed to add prokinetics (metoclopramide) to improve the oesophageal and gastric emptying and H2-blockers to avoid oesophageal ulcers [2]. At the refeeding, small volume meals are suggested [26]. The surgical approach for chronic GV is still controversial, but it is recommended if the conservative treatment fails. The procedure could be performed laparoscopically or via laparotomy, and, just as in the acute form, it consists of derotation of the stomach, anterior or fundal gastropexy, with or without a gastrostomy, and correction of coexisting anomalies. If GERD is diagnosed, fundoplication may be required.

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Part XXII

Mucosa-Related Gastropathology

Helicobacter-Related Gastritis and Ulceration and Investigation of *Helicobacter pylori*

119

Priya Narula

Introduction

Helicobacter pylori (*H. pylori*) infection occurs worldwide. Infection occurs most often in poor socioeconomic conditions and has been consistently linked to residential crowding and migration from high prevalence areas. Onset of infection occurs most frequently in childhood [1]. The mode of transmission of *H. pylori* has not been clearly identified. Evidence suggests that direct person-to-person transmission occurs, but the relative importance of the faecal-oral route or oral-oral route is not fully determined nor has the relevance of waterborne and zoonotic pathways been established [1]. Little is known regarding host factors that influence susceptibility to acquisition or persistence of infection.

H. pylori colonisation is the most common cause of chronic gastritis and is etiologically linked to gastric ulcer, duodenal ulcer, gastric adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma. Gastroduodenal diseases associated with *H. pylori* are typically manifested in adults but the infection is usually acquired in childhood, and it is possible that mucosal and humoral responses at this time may affect the course of natural infection.

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The Bacterium and Its Pathogenicity

H. pylori is a gram-negative spiral-shaped bacterium that colonises the human gastric mucosa and is consistently associated with the development of chronic gastritis [2]. Several genes of *H. pylori* have been identified as being virulence associated and may have clinical and epidemiological implications. The cytotoxin-associated (cagA) and the vacuolating cytotoxin (vacA) genes appear to be the most extensively studied. The cagA gene is present in some strains (50–60% of *H. pylori* isolates from Western countries and in >90% isolates from East Asian countries) and may have resulted from acquisition of DNA from other bacteria [3]. The vacA gene is present in a majority of strains and comprises two variable parts [4]. *H. pylori* vacA s1, vacA m1 and cagA positive genotypes have been associated with higher degrees of inflammation, atrophy and intestinal metaplasia and epithelial damage in adults [5]. Day et al. [6] demonstrated that cagE is an important virulence factor associated with duodenal ulcers in *H. pylori*-infected children. Rick et al. confirmed the association between gastric mucosal *H. pylori* cagA expressions and paediatric gastroduodenal ulcer disease using in situ hybridisation techniques [7]. However, in a study from China, cagA was not shown to influence the disease phenotype in children, and they had a higher prevalence of cagA+ strains compared to adults [8]. The impact of virulence factors, however, is only

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one of many factors including environment and genetic characteristics of the host that influence the clinical manifestations of infection.

Epidemiology

H. pylori infection is usually acquired in early childhood in both developing and developed countries [9, 10]. Prevalence rates vary and are higher in the developing countries. Sykora et al. [11] estimated a prevalence of 7.1 % in asymptomatic children in the Czech Republic, among the lowest reported in Europe. They found a positive association with increasing age, number of children in the household, lack of formal education of the father and institutionalisation. These findings are consistent with improving trends in living and housing conditions in recent years with decreasing family size.

While the prevalence is decreasing globally and is low in Western Europe and North America, prevalence remains relatively high in most Asian, South American, African and aboriginal populations [12–14]. In a study from Pakistan, a seroprevalence of 47 % was reported with the father's educational status, crowding and increasing age influencing seropositivity [15].

Intrafamilial spread by direct person to person contact is an important aspect or transmission [1, 16]. A recent study suggested that the older sibling may be an important source of *H. pylori* transmission when siblings are close in age [17]. The role of external reservoirs in *H. pylori* transmission has not been ruled out particularly in rural and developing areas [18]. Moderate support for potential waterborne transmission of *H. pylori* has been reported by Travis et al. [19] in a cohort study of 472 children from Mexico and Texas using UBT testing at 6-month intervals from birth to 24 months to describe possible waterborne transmission of *H. pylori*.

Clinical Manifestations

H. pylori infection in children is mostly asymptomatic and not associated with specific gastrointestinal symptoms.

Gastrointestinal Manifestations

Recurrent Abdominal Pain

The association between recurrent abdominal pain, epigastric pain, unspecified abdominal pain and *H. pylori* infection is not established. Whether *H. pylori* gastritis causes abdominal pain in the absence of peptic ulcer is not clear. Several studies have applied different non-invasive tests for *H. pylori* infection and compared the prevalence of positive results in children with recurrent abdominal pain and controls and found no significant difference in infection rates between cases and controls [20, 21]. A meta-analysis of 45 studies also concluded that *H. pylori* infection is not associated with abdominal pain [22]. More recently Tindberg et al. [23] reported no significant association of recurrent abdominal pain with *H. pylori* infection in 695 schoolchildren between 10 and 12 years of age. In fact an inverse association was noted, while recurrent abdominal pain was found unrelated to *H. pylori* infection when adjusted for age, gender and family background variables. And in another meta-analysis, Spee et al. [24] found no association between recurrent abdominal pain and *H. pylori* infection in children, conflicting evidence between epigastric pain and *H. pylori* infection and limited evidence for an association between unspecified abdominal pain and *H. pylori* infection in referred but not in primary care patients.

Several uncontrolled intervention studies show improvement in abdominal pain after *H. pylori* treatment. But in some studies, treatment success was not monitored and eradication of bacteria was assumed in cases of symptomatic improvement [25, 26]. And in other studies, follow-up period was a few weeks only [27]. In a small double-blind randomised placebo-controlled trial in 20 symptomatic children with *H. pylori* (excluding cases of peptic ulcer) followed up for 12 months, bacterial eradication and healing of gastric inflammation did not lead to symptomatic relief of chronic abdominal pain [28].

Therefore, in the absence of ulcer disease, there is inadequate evidence supporting a causal relationship between *H. pylori* gastritis and recurrent abdominal pain.

Peptic Ulcer

Compared to adults, peptic ulcer disease is found less often in infected children undergoing upper endoscopy. In a European multicentric study including 1,233 symptomatic children with *H. pylori* infection, peptic ulcer disease was diagnosed in less than 5 % of children under the age of 12 years and in about 10 % of teenagers [29]. However, *H. pylori* infection is an important cause of duodenal ulcers in children.

A causal relationship between *H. pylori* and duodenal ulcer disease in children has been demonstrated [30]. However, *H. pylori* is not the only aetiological factor as shown in a series of 37 children with gastric or duodenal ulcers, where *H. pylori* was detected in only 15 children [31]. Other aetiological factors were identified in 21 of remaining 22 children including Crohn's disease, coeliac and treatment with ulcerogenic drugs [31].

Rick et al. [7] investigated 51 children of whom 8 had gastric ulcers (6 *H. pylori* positive) and 11 had duodenal ulcers (10 *H. pylori* positive) and found expression of 16S rRNA and cagA was significantly higher in children with ulcer compared with normal children. A strong relationship between gastrointestinal bleeding because of duodenal ulcer disease and *H. pylori* infection in childhood has also been reported [32].

Gastro-oesophageal Reflux Disease

The role of *H. pylori* in gastro-oesophageal disease remains controversial, limited by sufficient published data in children. Recent studies do not report a consistent association between *H. pylori* infection and gastro-oesophageal disease [33, 34]. A retrospective analysis of 420 patients reported that there was a significantly higher prevalence of reflux oesophagitis in an *H. pylori*-infected cohort independent of age or sex suggesting that *H. pylori* infection in children is positively associated with reflux oesophagitis [33]. However, another retrospective analysis of 206 children did not show an increased prevalence of *H. pylori* infection in patients with gastro-oesophageal disease. A negative significant association was not found either between prevalence of *H. pylori* and erosive oesophagitis [34].

Gastric Cancer

Various epidemiological and intervention studies support a causal relationship between *H. pylori* infection and risk of gastric cancer and gastric mucosa-associated lymphoid tissue (MALT) lymphoma [35–37]. Meta-analysis estimates the risk of gastric cancer associated with *H. pylori* infection to be two- to sixfold [38, 39]. A meta-analysis also observed that infection with cagA-positive strains further increase risk for non-cardia gastric cancers by twofold over and above the risk associated with *H. pylori* infection alone [38]. Other factors such as genetic make-up of the host and environmental influences such as dietary salt intake also influence the risk of gastric cancer [40].

Both of these cancer types are extremely rare in children although there are a few case reports in literature [41, 42]. The risk of gastric cancer may be high in *H. pylori*-infected children in whom a parent has gastric cancer. This higher risk may be due to the child sharing similar genetic and environmental factors with the affected parent and may also have the same bacterial strain [43].

About 70 % of gastric MALT lymphomas can be successfully treated with *H. pylori* eradication. In patients with the translocation t (11;18) (q21;q21), a marker of *H. pylori* independency, chemotherapy can be considered in addition to *H. pylori* eradication [44].

Extraintestinal Manifestations

There is uncertainty whether *H. pylori* infection has a role in extraintestinal diseases, although such a role has not been ruled out. There is some evidence to support that treatment of *H. pylori* infection may lead to improvement in iron deficiency anaemia, but there is insufficient evidence supporting a causal relationship of *H. pylori* infection to otitis media, food allergy, idiopathic thrombocytopenic purpura and short stature [45].

Iron Deficiency Anaemia

H. pylori infection may be the cause of iron deficiency anaemia even in the absence of erosions or

ulceration [46, 47] or gastrointestinal symptoms [48]. Studies have shown an association between low iron status and *H. pylori* infection [49, 50] reporting enhanced iron absorption following eradication treatment for *H. pylori* [50]. In a randomised placebo-controlled study of 22 *H. pylori*-infected children and adolescents randomised into three treatment arms – iron only, eradication therapy only or both [50] – eradication therapy increased haemoglobin levels even without iron substitution, while iron therapy alone did not. In another study of 140 children between 6 and 16 years, recovery in iron deficiency and iron deficiency anaemia were achieved with *H. pylori* eradication without iron supplementation [51]. However, this beneficial effect was not confirmed in an intervention study in a high prevalence population, which did not show improvement in isolated iron deficiency or mild anaemia following treatment and resolution of *H. pylori* infection up to 14 months after treatment initiation [52].

No association between *H. pylori* infection and iron deficiency anaemia has also been reported [53, 54]. It can be difficult to distinguish between anaemia due to *H. pylori* infection and due to other confounding factors such as poor nutritional status or other underlying disease. Confounding by mutual risk factors may explain the observed association in the absence of a causal link.

Growth Failure

The link between *H. pylori* and poor growth remains weak. A cross-sectional study of Mexican school children from a low socioeconomic background found a negative association between *H. pylori* infection (based on 13C urea breath test) and height compared to uninfected matched controls and suggested the risk was greater in children above the age of 7 years [55]. However, an Australian cross-sectional study of refugee children from Africa failed to find an association between *H. pylori* infection and growth restriction [56]. Sood et al. compared height, weight and body mass index of 97 *H. pylori*-positive children with dyspeptic symptoms to 160 children with dyspepsia without infection. After adjusting for socioeconomic deprivation and ethnic difference, they found no significant difference between mean weight and height standard deviation scores in infected and noninfected group [57].

Diagnosis

Diagnostic tests for detection of *H. pylori* are classified as invasive and non-invasive tests. Invasive tests require gastric tissue for detecting *H. pylori* and therefore require performing an endoscopy and include histopathology, rapid urease tests, culture, PCR and fluorescence in situ hybridisation (FISH). Non-invasive tests include different methods of detecting *H. pylori* antigen in stool; detection of antibodies against *H. pylori* in serum, urine and salivary samples; and ^{13}C urea breath tests.

Invasive Tests

Histopathology (Figs. 119.1 and 119.2)

Performing an upper GI endoscopy in symptomatic children provides gastric biopsy tissue samples for testing for *H. pylori*. An endoscopy with histopathology not only detects *H. pylori* but also any lesions associated with the infection and any other possible causes for the patient's symptoms.

Samples sent for histology are usually formalin fixed and paraffin embedded, and a variety of stains including haematoxylin and eosin, special stains and immunohistochemistry have been used to detect *H. pylori*. The sensitivity ranges from 66 to 100% and specificity 94–100% in published series from children [58]. The density of *H. pylori* may be patchy and therefore sensitivity increases with the number of biopsies taken. The highest bacterial count is usually in the antrum but in patients on acid-suppressing agents, the bacteria may be found in the corpus. Adult studies recommend discontinuing acid suppressive agents such as proton pump inhibitors for at least 2 weeks prior to testing as bacterial density may be reduced [59].

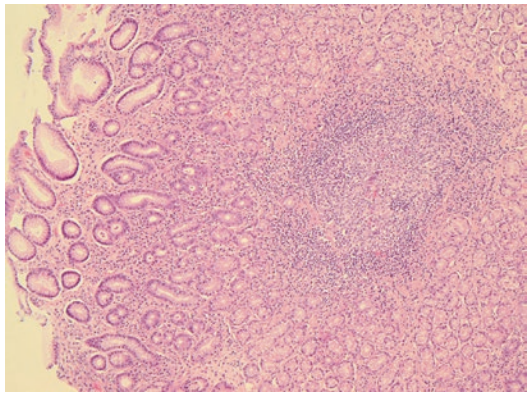

Fig. 119.1 *H. pylori* gastritis – active chronic inflammation in the antrum

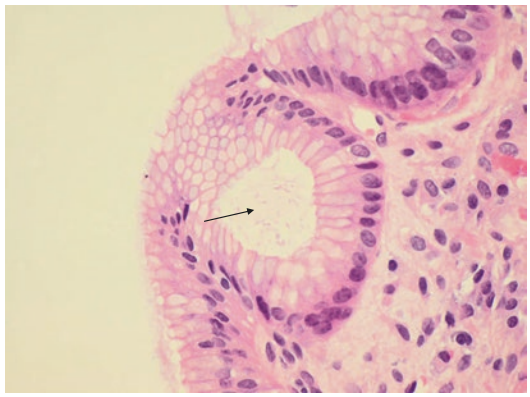

Fig. 119.2 *H. pylori* organisms in the mucous surface

Rapid Urease Test

Rapid urease test can be performed in gastric biopsy specimens using a wide variety of commercially available reagents. This test is based on the activity of *H. pylori* urease enzyme, which splits the urea reagent to form ammonia. Ammonia increases the pH, which is detected by the indicator phenol red. False-negative urease tests can be obtained in patients on proton pump inhibitors and adult studies recommend acid suppressants such as proton pump inhibitors for at least 2 weeks [59, 60].

A significant association between density of *H. pylori* organisms on histology and a positive rapid urease test has been noted [61]. The sensitivity of the rapid urease test varies from 75 to 100 % and specificity 84–100 % in published series in children [58].

Fluorescent In Situ Hybridisation (FISH) or Polymerase Chain Reaction (PCR)

An advantage of fluorescent in situ hybridisation and PCR is the ability of determining clarithromycin resistance in frozen or formalin-fixed paraffin-embedded tissues and does not depend on bacterial growth [62]. However, their use is currently limited as a research tool as it is technically demanding and expensive.

Culture

H. pylori can be cultured from gastric biopsies. The colonies are gram negative, urease positive, oxidase positive and catalase positive. This test has a 100 % specificity and is a reference standard but sensitivities can vary [63, 64]. Variable sensitivities may be due to insufficient number of biopsies, delay in transport, exposure to aerobic environment and also depend on laboratory experience.

Non-invasive Tests

Antibodies to *H. pylori* in Blood, Urine and Saliva

Due to a wide variability in the sensitivity and specificity for detection of antibodies (IgG and IgA) to *H. pylori* in serum, whole blood, urine and saliva in children, these assays cannot be used on their own in children and adolescents for either diagnosis of *H. pylori* infection or to monitor the success of therapy [45]. In addition, they do not distinguish between an active infection and a previous exposure to *H. pylori*. A positive IgG serology test can occur several months or years after infection and therefore cannot be used reliably for diagnosis or to confirm eradication [58].

^{13}C-Urea Breath Test

H. pylori produce urease, an enzyme that splits urea into ammonia and carbon dioxide. The urea breath test is based on the principle that urease activity is present in the stomach of infected individuals. Patients ingest urea labelled with ^{13}C. Hydrolysis of urea occurs within the mucus layer and results in the production of labelled CO_2. The CO_2 diffuses into the epithelial blood

vessels and soon appears in the subject's breath. Labelled urea is usually given to the patient with a test meal to delay gastric emptying and increase contact time with mucosa. After ingestion of urea, breath samples are collected for analysis.

^{13}C-Urea breath test is a simple and safe non-invasive test for detection of *H. pylori* in children older than 6 years of age before and after treatment (at least 4 weeks after stopping antibiotics and 2 weeks off proton pump inhibitors). The reported sensitivities of this test in published series in children range from 75 to 100 % before treatment and 94.1–100 % after treatment, while specificity ranges from 77.5 to 100 % before treatment and 92.3–100 % after treatment [58]. Several protocols can be used to perform this test though optimal conditions of this test in children less than 6 years of age require further evaluation [58].

Stool Antigen Detection

This is a simple, safe and convenient non-invasive test wherein samples can be easily obtained. Several methods are available for detection of *H. pylori* antigen in stool including enzyme immunoassay (EIA) based on polyclonal and monoclonal antibodies and immunochromatographic tests (rapid or quick tests).

A meta-analysis (including adult and paediatric studies) of stool *H. pylori* antigen detection using EIA with monoclonal and polyclonal antibodies demonstrated higher pooled sensitivity with monoclonal antibodies compared with polyclonal antibodies both before treatment (95 % versus 83 %) and after treatment (91 % versus 76 %) of *H. pylori*, thereby concluding that monoclonal EIA stool antigen tests were an accurate non-invasive test for initial diagnosis and confirmation of *H. pylori* eradication [65]. Sensitivities of the EIA monoclonal tests published in paediatric studies range from 96.6 to 98 % before treatment of *H. pylori* and 100 % after treatment while specificities range from 94.7 to 100 % before treatment and 96.2–100% after treatment [58]. An additional advantage is that the diagnostic accuracy of the EIA stool test does not appear to be age dependent [66].

Rapid faecal tests based on immunochromatography using monoclonal antibodies have a lower sensitivity compared to EIA with monoclonal antibodies, along with the disadvantage of interobserver variability and equivocal results [67, 68].

Indications for Treatment

A meta-analysis of studies looking at adult patients with peptic ulcer disease and *H. pylori* infection indicate that relapse rate of ulcers is high without treatment of *H. pylori* infection [69]. Recently published paediatric guidelines in line with this recommend eradication of the organism in *H. pylori* infection and peptic ulcer disease, healed ulcers and history of peptic ulcer disease [45].

If *H. pylori* is detected using biopsy-based methods in the absence of peptic ulcer disease, then treatment can be considered after evaluating the risks and potential benefits for the patient [45].

In the rare child with pathological evidence of MALT lymphoma or atrophic gastritis with intestinal metaplasia, who has coexisting *H. pylori* infection should be treated with eradication therapy [70]. Treatment can also be offered to children infected with *H. pylori* who have a first-degree relative with gastric cancer [45].

Treatment

Choosing an appropriate eradication regimen will not only ensure eradication of *H. pylori* but may also prevent the development of antibiotic resistance and subsequent spread of resistant strains.

A combination of proton pump inhibitors and two antibiotics (usually clarithromycin or metronidazole in conjunction with amoxicillin) has been recommended as first-line eradication for *H. pylori* in treatment in various paediatric guidelines [70, 71]. A prospective randomised double-blind trial comparing dual therapy of amoxicillin and clarithromycin with triple therapy including omeprazole demonstrated that triple therapy

achieved higher eradication rates of 74.2 % compared to 9.4 % with dual therapy [72].

A meta-analysis of randomised controlled trials that compared duration of eradication therapy concluded that extending triple therapy beyond 7 days was unlikely to be clinically useful [73]. Bismuth-based triple therapy is an alternate first-line therapy. A study by the European paediatric treatment registry reported bismuth-containing triple therapies were more effective than proton pump inhibitor containing ones (77 % versus 64 %). However bismuth's palatability affecting adherence is a concern [74].

A meta-analysis of *H. pylori* eradication treatment efficacy in children concluded that overall the methodological qualities of the studies was poor with small sample sizes and few randomised controlled trials and highlighted the need for additional well-designed randomised trials in children [75]. Therefore most evidence is obtained from adult studies.

Development of antibiotic resistance may adversely affect the eradication rates. Non-adherence to treatment is also a well-recognised factor in failed eradication but is difficult to measure in clinical trials. *H. pylori* resistance to antimicrobials can be either primary (i.e. existing before *H. pylori* treatment) or secondary (i.e. developing as a result of failed therapy). Wide use of these antibiotics has led to a significant increase in resistance to clarithromycin and metronidazole and is reported in several studies with overall rates as high as 24 % in Europe [29, 76, 77]. The use of antibiotics for other indications appeared to be a major risk factor for development of primary resistance. Overall resistance to clarithromycin was found in 24 % (mean primary resistance 20 %, mean secondary resistance 42 %) and overall resistance to metronidazole was 25 % (primary resistance 23 %, secondary resistance 35 %). While resistance to both antibiotics was noted in 6.9 % (primary resistance 5.3 %, secondary resistance 15.3 %) and resistance to amoxicillin was only 0.6 % [29].

Clarithromycin resistance is highly predictive of treatment failure if clarithromycin is part of the treatment regime [78], and therefore clarithromycin-based triple therapy should be used as first line guided by susceptibility testing or if clarithromycin resistance rates are low. Treatment directed by antibiotic susceptibility testing results in highly effective eradication rates [79].

Antimicrobial drug resistance therefore is a major cause of failure of *H. pylori* eradication and is responsible for a decline in eradication rate. Declining eradication rates with standard triple regimens have led to the development of alternate treatment options. Sequential therapy is a promising alternative for eradication of *H. pylori*. Sequential therapy involves dual therapy with proton pump inhibitors and amoxicillin for 5 days followed sequentially by 5 days of triple therapy (a proton pump inhibitor with clarithromycin and metronidazole/tinidazole). The mechanism of action of sequential therapy is unclear but the initial therapy with amoxicillin might reduce the bacterial load in the stomach, and this in turn may improve the efficacy of the subsequently administered triple therapy. It has been suggested that sequential therapy may be more effective than standard triple therapy because it involves the administration of four drugs (i.e. proton pump inhibitor and three antimicrobials) with an additional antimicrobial compared to triple therapy. Although, most of this data is from Italian studies and therefore further assessment across a broad range of patients is required before sequential therapy could replace standard treatment regimens. In addition, it is not clear whether it is necessary to give the drugs sequentially or if the four components can be given concurrently as quadruple therapy as that would be less complex for the patient [80].

A meta-analysis of randomised controlled trials (most trials carried out in Italy) in adults and children concluded that sequential therapy was better than triple therapy in eradication of *H. pylori*. It highlighted the need for further trials in other European countries and North America before it can be recommended as first line [81]. Another meta-analysis had similar results showing sequential therapy was superior to standard triple therapy for eradication in treatment-naive patients even when there was evidence of clarithromycin resistance [82].

A prospective randomised trial in adults concluded that in geographical areas with high (>15 %) prevalence of *H. pylori* strains resistant to clarithromycin, a levofloxacin-containing sequential therapy is more effective (96 % eradication rate compared to 80.8 %), equally safe and cost saving compared to a clarithromycin-containing sequential therapy [83]. There has however been a rapid emergence of resistance to levofloxacin, and in some parts of Europe, high prevalence of levofloxacin-resistant strains has been described [84].

In an open multicentric trial involving 62 children with metronidazole- and clarithromycin-resistant *H. pylori*, eradication was achieved in 66 % with high-dose amoxicillin, metronidazole and esomeprazole for 2 weeks [85].

In recently published paediatric guidelines [45], triple therapy or sequential therapy is recommended as first-line eradication regime. In addition, antibiotic susceptibility is recommended for clarithromycin prior to initial clarithromycin-based triple therapy in populations with high rates of *H. pylori*-resistant strains (>20 %). Post treatment a reliable non-invasive test (^{13}C-urea breath test or monoclonal EIA faecal antigen test) is recommended at least 4–8 weeks following completion of eradication treatment.

In cases of treatment failure, repeat endoscopy with culture and antibiotic sensitivity testing can be performed to guide second-line therapy, or FISH can be used to detect primary clarithromycin resistance in previously obtained biopsies. If not possible then, treatment can be modified by adding an antibiotic or bismuth (quadruple therapy) or using antibiotics not used in initial regime (including levofloxacin in triple therapy) and/or giving a larger dose and/or longer duration of eradication treatment up to 14 days [45].

Conclusion

Helicobacter pylori is the most common cause of chronic gastritis and an important cause of gastric and duodenal ulcers. It is usually acquired in early childhood and intrafamilial spread is an important aspect of transmission. Diagnosis is made by biopsy-based tests. *H. pylori* is eradicated using triple therapy or sequential therapy and eradication is confirmed with a reliable non-invasive test. In cases of treatment failure, antibiotic susceptibility testing may be helpful.

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Non-*Helicobacter pylori* Gastritis, Ulceration, and Drug-Related Gastropathies

120

Arun Nanjundaraje Urs

Introduction

Helicobacter pylori infection is the most common cause of gastritis in children and associated with duodenal ulcer [1]. Due to improved socioeconomic conditions, widespread use of effective treatment and pervasive use of antibiotics for unrelated conditions may be some reasons for steady decline in prevalence of *H. pylori* infections [2]. This has led to increasing reports of *H. pylori*-negative gastritis and other causes of gastritis [3]. Although gastritis is a frequent endoscopic or histopathologic finding in children, peptic ulceration of the stomach or duodenum is very uncommon [4].

In this chapter, we aim to provide a structured approach for evaluation of non-*Helicobacter pylori* gastritis, ulceration, and drug-related gastropathies. The aspects of *H. pylori* infection, associated ulcer disease, and systemic diseases affecting the stomach are discussed elsewhere.

Gastritis refers to the presence of inflammatory cells in the gastric mucosa and precludes mucosal ulceration. Gastritis is mostly a histological term that needs biopsy to be confirmed and often appears normal at endoscopy. The epithelial cell damage and regeneration with minimal or no associated inflammation are referred to as "gastropathy" with typical endoscopic features as described by some authors [5]. There is no universally accepted classification, which can provide a satisfactory description of all types of gastritis or gastropathy and also due to different objectives. The upgraded Sydney systems have been widely adopted in adults however and have little broad application to children [6, 7]. The etiology-based classification provides an understanding of natural history of lesion and a practical approach for further investigation and management [8] Table 120.1.

Classification of Gastritis (Table 120.1)

Non-*Helicobacter pylori*-Negative Gastritis

H. pylori has been regarded as the main cause of chronic active gastritis [9] for nearly three decades. True *H. pylori*-negative gastritis is a chronic active inflammation of gastric mucosa with no detectable *H. pylori* organisms. There is perceived belief among the pathologists in the Western world that "*H. pylori*-negative chronic active gastritis" is increasing. Genta et al. performed a database review on 102,497 gastric biopsies of which 10,517 had a diagnosis of chronic active gastritis. In 1,933 cases (18.6%), no *H. pylori* organisms were visualized and of which <10% of cases remain apparently

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Table 120.1 Classification of gastritis and gastropathy in children

Infectious
Bacterial
Helicobacter pylori (common)
Non-*H. pylori*, *Helicobacter* species, or other *Helicobacter*
Mycobacterial
Viral
Parasitic
Fungal
Granulomatous gastritis
Noninfectious
Infectious
Idiopathic
Reactive gastropathy and drug-induced gastropathies
Drugs including NSAIDs
Bile reflux
Stress
Others (exercise, radiation, corrosive, traumatic, neonatal)
Allergic gastritis
Lymphocytic gastritis
Celiac disease
Other causes
Immune-mediated gastritis
Autoimmune gastritis
Autoimmune endocrinopathies
Graft-versus-host disease
Vascular
Henoch-Schonlein purpura
Portal hypertensive gastropathy
Other forms of gastritis
Collagenous gastritis
Uremic gastropathy
Hyperplastic

unexplained [10]. The prevalence and severity of chronic gastritis in *H. pylori*-negative patients with gastrointestinal disorders are more common than previously appreciated and called for better characterization of gastric mucosal histology [11]. Although the etiology of chronic gastric inflammation in the absence of *H. pylori* infection remains unknown, it is believed that "incidental antibiotic treatments" are one of the most common causes of *H. pylori*-negative gastritis along with masking effect of proton pump inhibitors (PPIs) and inadequate sampling or suboptimal staining techniques. A meticulous search for *H. pylori* is merited before a diagnosis of *H. pylori*-negative chronic active gastritis.

Helicobacter heilmannii Gastritis

Dent et al. [12] and McNulty et al. [13] reported the presence of a new spiral bacterium, *Helicobacter heilmannii*, formerly known as *Gastrospirillum hominis*, in the gastric mucosa of three adults with chronic gastritis. *H. heilmannii* infection has since been reported, although rarely, in children [14]. *H. heilmannii* microorganisms are gram-negative bacilli, measuring up to 1.0 μm wide and 5.0–10.0 μm long as opposed to smaller, curved, and less spiral *H. pylori*. Most species possess strong ureolytic ability, particularly those associated with gastric mucosa [4]; this is the basis of identifying the organisms by rapid urease test. *Helicobacter heilmannii* (previously *Gastrospirillum hominis*) is probably transmitted from cats and dogs [15, 16] and may cause chronic active gastritis similar to that of *H. pylori* but with less severe inflammation [17, 18]. However, as yet, a definite association between *H. heilmannii* infection and ulcer disease has not been established [19]. In populations living in North America and Europe, the prevalence of infection is between 0.3 and 1.1 % of the general population [17, 20–22]. In populations living in Southeast Asia, the infection rate may be as high as 6 % [23]. *H. heilmannii* appears to be acquired by human contact with farm animals and household pets [24]. The characteristic spiral organisms are readily identified by the same range of special staining techniques employed for identification of *H. pylori* [23]. Some patients benefit symptomatically from antibiotic treatment [20]. Persistence of *H. heilmannii* has been recorded in children after successful eradication of *H. pylori* and has necessitated further antibiotic therapy [7, 8]. Rarely, other helicobacter species have been isolated from the stomach.

Other Bacterial Causes of Gastritis

Gastric Tuberculosis

The gastric tract is an uncommon site of extrapulmonary tuberculosis infection, even in parts of the world where intestinal tuberculosis is common. The incidence of gastric tuberculosis is 0.03–0.21 % of all routine autopsies [25]. The rarity of gastric tuberculosis is due to gastric acid, continuous motor activity of the stomach, and the scarcity of lymphatic follicles in the gastric wall [26]. Gastric tuberculosis usually develops secondary to other tuberculous lesions, most commonly pulmonary [27]; nonetheless, sporadic cases of primary gastric tuberculosis have been reported worldwide [9–14]. The possible routes of infection include direct infection of the mucosa, hematogenous spread, or extension from a neighboring tuberculous lesion [26]. Gastric tuberculosis is usually associated with an immune-deficient state [27]; many cases reported in developed countries are in immunodepressed patients, particularly those with HIV infection. But such relationships have not been well described in cases reported from developing countries. The clinical manifestations of this type of infection are nonspecific. Consequently, diagnosis is often missed. There are reports of isolated gastric tuberculosis presenting as pyrexia of unknown origin [28]. Other presentations include gastric carcinoma [17], gastric outlet obstruction [18], benign peptic ulcer [19], and, rarely, stomach perforation [20]. Based on endoscopy, lesions may be described as single or multiple ulcers and hypertrophic nodular lesions surrounding a stenotic pyloric channel [29]. The antrum and prepyloric regions are the most common sites of tuberculous lesions in the stomach [25]. The diagnosis of gastric tuberculosis can only be made by histological study of the resected stomach or of a biopsy specimen of this organ. Endoscopic brush cytology and biopsy are only occasionally successful in diagnosis [30]. Submucosal location of the lesion has been cited as a reason for failure of endoscopic biopsies [28, 31]. On biopsy, granulomas are either caseous or non-caseous. Staining for acid-fast bacilli is frequently negative, and the diagnosis is either by culture or finding of confirmed tuberculosis elsewhere [32].

Viral Gastritis

Several viruses infect the stomach; most importantly CMV and others that are isolated include EBV, herpes virus, hepatitis C, measles, varicella, human herpes virus 6, and influenza; and the latter can be associated with severe hemorrhagic gastritis [33].

Cytomegalovirus (CMV) and Gastritis

CMV gastritis occurs mainly in immunocompromised children and adults, such as those with malignancies, immunosuppression (steroids), posttransplant, or AIDS [34] and who are at risk of disseminated and or symptomatic CMV disease. Less commonly, CMV infection occurs in immunocompetent patients [35]. CMV is associated with childhood Ménétrier disease (associated with protein losing enteropathy), which causes significant morbidity in infants/children. Most children recover spontaneously or with supportive care. However rarely, antiviral-specific therapy is required [36–38]. Endoscopically, the mucosa is commonly congested and swollen rugal folds with multiple erosions and ulcerations [39] in the gastric fundus and body. The diagnosis may be established by immunohistochemical detection of CMV early nuclear antigen in gastric biopsy [36]. Detection of CMV DNA in a gastric biopsy sample by PCR is a more sensitive assay than antigenemia and serology tests, as it detects a disease localized to the gastrointestinal tract [40]. The examination of biopsies reveals mixed inflammatory infiltrate and characteristically enlarged endothelial, stromal, or epithelial cells with owl's-eye intranuclear inclusions. However, this highly specific appearance may be difficult to identify. Instead, granular

basophilic cytoplasmic inclusions may be seen. The inclusions in the endothelial cells are best observed when the mucosa is not ulcerated. Alternatively, they are commonly noted in the mesenchymal cells (endothelial and stromal) when the mucosa is ulcerated [41, 42]. The early detection of CMV infection and the early initiation of antiviral therapy for those patients at high risk for CMV infection are very important to reduce the risk for CMV disease and CMV-associated death [43], but otherwise spontaneous recovery usually occurs within 1–2 months [37].

Epstein-Barr Virus and Gastritis

EBV gastritis is rarely recognized with only five reported cases in the literature. The endoscopy revealed several ulcerative lesions and diffuse gastritis [44–47] with dense and diffuse lymphoid infiltrate with atypical lymphocytes. Clinical correlation is required to exclude malignant lymphoma. The in situ hybridization techniques are very useful in diagnosing EBV-associated gastritis and spontaneously resolve with symptomatic management.

Parasitic Gastritis

Anisakiasis

Parasitic disease that affects the stomach is acquired by ingestion of raw or inadequately cooked fish that contains larval nematodes. Once the parasite is ingested, it can migrate back to the esophagus and be expectorated, invade the mucosa of the stomach or intestine, or be excreted in the stools. In the stomach, the parasite can cause severe epigastric pain, nausea, vomiting, and diarrhea within 1–24 h after eating raw fish or can cause chronic intermittent abdominal pain, nausea, and vomiting that can be present for weeks or months [33]. In some patients with anisakiasis, an acute allergic reaction can occur, with urticaria, angioedema, erythema, bronchospasm, and anaphylaxis [48]. Removal of the parasite through endoscopy is curative and is associated with eosinophilic gastritis.

Gastric Giardiasis

Giardia is a flagellated, binucleated protozoan and is one of the most common small intestinal parasites and is found worldwide. GG is uncommon and fewer than 90 cases have been reported in literature [49]. GG is usually seen in the antrum, probably as a result of biliary reflux, and is usually associated with *H. pylori* infection. Conditions of increased gastric pH such as hypochlorhydria (primary or secondary to medications), partial gastrectomy, atrophic gastritis, or biliary reflux can result in *Giardia* colonization of the gastric epithelium. It has been reported that GG can be induced by the use of PPI therapy, and the infection can disappear within 4 weeks of stopping PPI therapy without any specific therapy for GG [50]

Other Parasitic Gastritis

Cryptosporidiosis [51], toxoplasmosis [52], and visceral leishmaniasis [53] are isolated from the stomach, particularly in AIDS patients. These common opportunistic infections have a wide variety of endoscopic appearances and only histologic examinations of biopsy specimens allows for specific diagnosis. The stomach is also rarely affected by *Strongyloides stercoralis*.

Fungal Gastritis

Candida, *Aspergillus*, *Histoplasma*, and *Mucor* may occur in children with burns, malnourishment, and in those who are immunocompromised. Candida species are frequent pathogen demonstrated frequently from gastric ulcers of both immunocompetent and immunosuppressed patients [54]. Invasion of the gastric mucosa by organisms can define whether there is colonization or infection [33]. Gastric phycomycosis is another rare condition, highly lethal in its invasive

form, and characterized by deeper invasion of the gastric wall and blood vessels [55]

Phlegmonous Gastritis and Emphysematous Gastritis

Phlegmonous (suppurative) gastritis is a rare rapidly progressive condition characterized by bacterial infection of the gastric submucosa resulting in necrosis and gangrene [56]. Phlegmonous gastritis is a rare disease with only few reported cases in adult literature occurring in a background of preexisting disease conditions such as alcoholic liver disease, acquired immune deficiency syndrome, and other immunocompromised states [57, 58]. It is most commonly associated with alpha- or beta-hemolytic streptococci (70%), but pneumococci, *E. coli*, *Staphylococcus aureus*, *Proteus*, and *Clostridium welchii* are also isolated [56]. There are reports associated with *Helicobacter heilmannii* in children [59] and in an infant [60]. Endoscopically, the stomach appears edematous with multiple perforations, and the mucosa tends to have a granular green-black exudate. Histologically, an intense neutrophilic collection consistent with pus is seen. The treatment includes surgical resection and drainage of stomach with systemic antibiotics. The mortality rate is still greater than 60% despite aggressive use of antibiotics due to delay in diagnosis and initiation of management (Mittleman and Suarez [57]).

Emphysematous gastritis is a rare but severe form of phlegmonous gastritis, characterized by intramural gas of the stomach due to invasion by gas-forming microorganisms. It is extremely uncommon in stomach compared to other hollow organs [61]. The condition is often lethal, and early recognition and treatment offer the best chance of survival (Huang and Liao 2009).

Reactive Gastropathy

Also described as chemical or reactive or reflux or and type C gastritis. It is one of the most common diagnoses on gastric biopsies in North America [62]. It is a well-described histopathologic entity in adults characterized by foveolar hyperplasia with edema, smooth muscle hyperplasia, and congestion of superficial capillaries in the lamina propria in the absence of significant inflammation [63, 64]. This distinctive histological picture seen in reactive gastropathy is considered to be a nonspecific response to variety of gastric irritants, including bile [65]. The endoscopic features of this entity are vague and may include erythema and ulcerations. Reactive gastropathy is most often associated with either medications (especially NSAIDs) or bile reflux. The prevalence of reactive gastropathy in patients taking NSAIDs is estimated between 35 and 45%. A nationwide database review was performed during a 12 months period in American patients, who had a gastric biopsy with a histologic diagnosis of reactive gastropathy. All patients were stratified by age. The prevalence of reactive gastropathy was 10.5% in children and dyspepsia was the most common indication. Despite its known association with NSAIDs and bile reflux, highlights of the possibility of other factors capable of evolving into reactive gastropathy need to be explored [66]. Pashankar et al. reported the risk factors in their survey of 21 children over a 3-year period were gastroesophageal reflux disease and intake of multiple medications, including nonsteroidal anti-inflammatory drugs [67].

Drug-Induced Gastropathies

There are number of drugs implicated to cause erosions or ulcers or reactive gastropathy of the stomach. Although it is not uncommon, it is generally underreported. They generally cause nonspecific injury pattern, but some of the drugs produce specific injury patterns to be recognized on histology. One of the earliest agents reported is potassium chloride, which causes ulcers and strictures throughout the GI tract [68, 69]

NSAIDs

NSAIDs are one of the most widely available and invaluable drugs for treatment of many disorders

in children and adults. The pathogenesis of NSAID-induced gastroduodenal mucosal injury is complex [72, 73]. The dual-injury hypothesis suggests that both NSAID-mediated direct acidic damage and the suppression of prostaglandin synthesis are necessary to induce gastric damage [72]. The topical irritant effects on stomach and prostaglandin suppression play a role in the pathogenesis of NSAID toxicity [70]. Even a single dose of aspirin may cause petechial hemorrhages in the stomach within a few hours and erosions within 24 h [71]. NSAIDs inhibit COX, especially COX1, which is constitutively expressed in normal GI mucosa decreasing the synthesis of mucosal prostaglandins and thereby interfering with mucosal blood flow. Initially, the acidic properties of NSAIDs induce topical mucosal injury to the gastroduodenum. The active hepatic metabolites of NSAIDs and the NSAID-related decrease in gastric mucosal prostaglandins indirectly contribute to cause gastroduodenal mucosal injury [72, 73]. When the hepatic metabolites in the bile are secreted into the duodenum, they cause mucosal damage to the stomach by duodenogastric reflux and to the small intestine by antegrade passage through the GI tract (Wolfe et al. [73]). Up to 45 % of patients who consume NSAIDs will develop chemical gastritis or reactive gastropathy [74, 75]. NSAID erosions are usually in the gastric body and heal within days, whether or not the NSAID is continued, whereas NSAID ulcers are often large and multiple, more commonly in the gastric antrum than in the duodenum, and painless [76, 77]. In children, hemorrhagic antral gastropathy and ulceration of the incisura are the typical NSAID lesions. Occasionally, more extensive gastric involvement occurs, as does duodenal ulceration. Bleeding from such lesions after ingestion of NSAIDs in children has been well documented [78–81].

Other Common Drugs

Iron: Characteristic brown crystalline material can be found in the lamina propria, in surface exudates, and, less often, in thrombosed vessels; the deposits are highlighted by Perl's Prussian blue stain [82–85]. In most cases, the iron is associated with erosions or ulcers. A pattern of reactive gastropathy or chronic gastritis may be noted in some cases [85, 86].

Many other drugs have been implicated to cause erosions, ulcer, and hemorrhagic gastritis such as colchicine, steroids, valproic acid, alcohol, and chemotherapeutic agents.

Stress Gastritis/Ulceration

Stress-induced gastritis, also referred to as stress-related erosive syndrome, stress ulcer syndrome, and stress-related mucosal disease, can cause mucosal erosions and superficial hemorrhages in patients who are critically ill or in those who are under extreme physiological stress, resulting in minimal-to-severe gastrointestinal blood loss and leading to blood transfusion if not addressed. Patients who may have an increased risk of stress gastritis are those with massive burn injury, head injury associated with raised intracranial pressure, sepsis, and positive blood culture results, severe trauma, and multiple system organ failure. A cohort of 1,006 consecutive admissions enrolled in a pediatric ICU reported that 10.2 % of pediatric participants had UGI bleeding and 1.6 % had clinically significant UGI bleeding [87]. A number of risk factors have been described, but respiratory failure, coagulopathy, and a Pediatric Risk of Mortality Score of $\geq$10 are independently associated with clinically significant upper GI bleeding [87–90]. Based on those findings, authors recommended that prophylaxis to prevent UGI bleeding may be limited to patients who present with at least two risk factors [87]. A guideline on stress ulcer prophylaxis published in 2006 recommended pharmacologic intervention in adults admitted to the ICU who have coagulopathy, require mechanical ventilation for >48 h, have a history of gastrointestinal ulceration or bleeding within 1 year before admission, or have at least two of the following risk factors: sepsis, ICU stay of >1 week, occult bleeding lasting ≥6 days, and use of >250 mg of hydrocortisone or the equivalent [91].

Unfortunately, there is still conflicting evidence concerning prophylaxis for stress ulcers in children with no systematic review on this topic [92].

Corrosive Gastropathy

Accidental corrosive ingestion is one of the common problems in children worldwide [93]. In teenagers and adults, alkali poisoning is more likely to occur as a form of deliberate self-harm and is associated with a higher mortality [94]. Caustic ingestion is seen most often in young children between 1 and 3 years of age [95], with boys accounting for 50–62 % of cases [96, 97]. Early signs and/or symptoms may not correlate with the severity and extent of tissue injury. In a review in which flexible endoscopes were used to evaluate 156 children with caustic ingestion, 17 (11 %) had esophageal and gastric burns, and 14 (9 %) had gastric burns only [98]. Gastric injury often is most severe with acids, such as sulfuric acid, which (because of pooling in the antrum and antral spasm) may cause severe burns in the prepyloric area, potentially leading to pyloric obstruction [99]. Acids generally cause coagulation necrosis, with eschar formation that may limit substance penetration to superficial layer of the esophagus [100]. Alkalis in contrast combined with tissue proteins cause liquefactive necrosis and saponification and are thought to penetrate deeper into tissues [101]. Alkali causes more damage to the esophagus, while acid ingestion tends to result in more severe gastric injury. However, deliberate ingestion of large quantities of alkali may injure the stomach and even the small intestine. Gastric injury is more likely to follow ingestion of a liquid than solid alkali [94].

Bile Gastropathy

Duodenogastric reflux results from retrograde flow of duodenal secretions through the pylorus into the stomach. Duodenogastric reflux (DGR) can be classified to two types, primary DGR or secondary DGR. The pathogenesis of primary DGR is not totally understood; possible hypotheses are disorders of gastric or duodenal motility, incompetent pyloric sphincter, and the gut hormone secretion. Secondary DGR is due to the operative stoma of the stomach, duodenum, and gall bladder [102]. Duodenogastric reflux (bile reflux) can cause gastric mucosal inflammation and/or ulceration [103], intestinal metaplasia in the stomach [104], and increased risk of gastric cancer [105]. DGR could cause hyperemia and erosions of gastric antral mucosa under endoscopy and gastric antral intestinal metaplasia histologically in children [106]. DGR is difficult to diagnose as the clinical symptomatology and endoscopic and histological features are nonspecific. The other different investigative methodologies such as measuring the concentrations of bile acids [107] and sodium in gastric contents [108], pH-metry [109], Doppler ultrasonography [110, 111], and dynamic cholescintigraphy are however helpful but not easily available in children.

Radiation Gastropathy

This is rare but has been associated with massive abdominal irradiation given to patients with malignancy, causing erosions or ulcers particularly in the gastric antrum and prepyloric regions.

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121 Long-Term Effects of Achlorhydria on the Stomach (*Helicobacter pylori* and PPI Therapy)

Marta Tavares and Jorge Amil Dias

The stomach has had an increasing importance in the GI tract pathology due to the multiple consequences of acid production that go well beyond the nutritional functions.

Processing ingested food is a major function of the stomach through mechanical physiology using kinetic tridimensional muscular structure and also through secretion of hydrochloric acid with pH between 1.0 and 3.5. Extreme acidity is produced by oxyntic cells located in the stomach fundus and body. These cells actively transport chloride and hydrogen ions into the glandular lumen in a mixture with pH 0.8 allowing persisting maintenance of acidity in gastric lumen with various consequences:

1. Activation of a proenzyme, pepsinogen, secreted by pyloric glands located in the antrum thus transforming it into an active enzyme that catalyses the hydrolysis of protein macromolecules.
2. Optimisation of enteric absorption of vitamins and minerals like vitamin B12 which requires intrinsic factor (IF) to promote absorption. IF is produced in antrum cells when the pH is low. Acidity of the stomach is very important for transformation of ingested iron from ferrous to ferric form and maintenance of chemical stability allowing subsequent intestinal absorption. Active secretion of ascorbic acid from plasma into gastric juice enhances this reaction and iron absorption. Acid pH is also needed to ionise calcium carbonate and transform it into ionised form to be absorbed.
3. In addition to the above-mentioned nutritional benefits, the gastric microenvironment has a relevant role as an antimicrobial defence barrier thus protecting the gastrointestinal tract from various ingested germs. The acid gastric pH is one of the most relevant non-specific defence mechanisms of the body [1]. In vitro studies have shown that pH 3 or below causes a bacterial depletion that lasts for 15 min, and bactericidal properties are kept when pH rises up to 4 [2]. Studies conducted in rats and subsequently confirmed in humans revealed that gastric juice is almost sterile, having a bacterial colony count below 10^5/ml [3]. Additionally to the chemical bactericidal properties, the acid causes closure of the pylorus inhibiting gastric motility, and this allows the gastric alimentary content to be kept for a considerable period of time exposed to these conditions. Therefore it potentiates the bacterial clearance and sterilisation of alimentary contents that passes into the gut where mucosal permeability is much higher.
4. Acid pH inhibits the growth of nitrites and other N-containing compounds generated from protein digestion. N-containing products are transformed into nitrates that are also

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secreted by the oral glands. Its conversion into nitrites involves some toxicity and may have a role in gastric epithelium metaplasia. This experimental evidence seems to have clinical confirmation from studies of gastric metaplasia performed in adults [4]. Thus, production of nitrous compounds in neutral pH may have some carcinogenic effect as seen in adults with chronic atrophic gastritis and persistent hypochlorhydria [5].

Maintenance of pH below 4.0 is due to the secretion of gastrin by the parietal cells. This is an important secretagogue produced by G cells, part of the pyloric glands located in the antrum. Emotional factors, initiation of the cephalic phase of digestion or any other vagal stimulus, as well as the presence of proteins in the gastric lumen, initiate the secretion of gastrin. Due to this mechanism, whenever there is a decrease in the production of acid, be it disease or ingestion of inhibitors of the parietal cells, there is a compensatory hypergastrinaemia. The production of gastrin is the strongest stimulus for the secretion of hydrochloric acid. Fortunately it is accompanied by the secretion of mucus that is essential to keep homoeostasis in the mucosal barrier.

Disturbance or variation of the gastric acidity can be divided into hyperproduction of acid causing a reduction of the pH, termed hyperchlorhydria, or reduction of the secretion, causing hypo- or achlorhydria. This is defined as a persistent pH above 6.5 after maximum stimulation with pentagastrin, synthetic analogue of the gastrin hormone. In paediatrics hyperchlorhydria may present as gastro-oesophageal reflux and oesophagitis, duodenal ulceration or gastritis, representing disruption of the mucosal barrier. In hypochlorhydria pH is usually between 4.0 and 6.5 and may be due to several causes as discussed below.

Causes of Hypochlorhydria in Children

Helicobacter pylori

Hypochlorhydria had much attention in the 1980s due to the identification of a cause for a well-known disease, epidemic hypochlorhydria affecting the adult population [6]. The hypothesis of a gram-negative bacillus similar to *Campylobacter* can be the causing agent for this condition and lasting for several months gained consistency after identification of *Helicobacter pylori* (Hp) [7]. The identification of this agent led to the award of the Nobel Prize in 1982. *Helicobacter pylori* became one of the most important digestive pathogens due to its ubiquitous nature and the large spectrum of effects that it may cause. It is an infective agent transmitted by enteral route, acquired early in infancy with compensatory hypergastrinaemia and has a worldwide distribution, especially in areas with low sanitary conditions. In paediatrics this is the most common cause for hypochlorhydria, being apparently as prevalent as malnutrition in some areas of the world. Infection is usually acquired in childhood and persists throughout life if not eradicated. Actual numbers of prevalence vary in different series and countries, being estimated as 20 % in population below 20 years in developed countries but also reported to occur in up to 85 % in children of 9 years of age [8]. In developing countries prevalence is also very high. Following infection with Hp and ensuing gastritis, there is a state of hypochlorhydria that may last for 8 months or more, and then pH subsequently becomes normal to previous acidity level. In adults chronic infection transforms the acute gastritis into chronic atrophic gastritis of the gastric body and antrum leading to irreversible hypochlorhydria and its consequences. The impact of gastric infection by Hp is mediated by inflammatory responses that are host dependent. Interleukin 1β (IL-1β) and TNF-α are potent inhibitors of acid secretion, and its variation leads to interindividual differences. Hypochlorhydria associated to Hp infection is dependent on the IL-1β polymorphisms in the population, with higher inhibition of secretion in carriers of genotypes IL-1B-511 C/T and T/T (strong producers of IL-1β) opposite to carriers of genotype IL-1B-511 C/C (weak producer of IL-1β) [9]. Variation of infecting Hp strains (like *cag*-positive strains that are more aggressive) is also associated with different degrees of hypochlorhydria in the host [10].

Other Infections

As mentioned above, hypochlorhydria favours proliferation of pathogens in the gastrointestinal tract. However, some infections, particularly in the mucosa of the gut, reduce acid secretion and may lead to hypo- or achlorhydria. Experimental studies in awake dogs have shown that stimulation with lipopolysaccharides from *Pseudomonas aeruginosa* causes reduction of acid secretion [3]. Infection with *Taenia taeniaeformis* in rats led to reduction of parietal cell mass, and it was postulated that this direct action on the gastric mucosa might facilitate the passage of the organism into the small intestine to adhere and proliferate. The hypothesis that a parasitic infection may cause transient hypochlorhydria in humans was confirmed with exposure to *Diphyllobothrium latum* and *Trypanosoma cruzi* by mechanisms yet unknown. In humans and experimental animal models in dogs, the transient inhibition of gastric secretion was observed after raising the body temperature to 39 °C by exposure to heated environment. In some infections there seems to be a reduction of acid secretion that returns to normal after the acute event.

Use of Inhibitors of Acid Secretion

Some diseases like duodenal ulcer or reflux oesophagitis are caused by the aggression of gastric acid on the mucosa and often require the use of medication to control it. The knowledge of pharmacological blockage of the acid was very well documented in adults with Zollinger-Ellison syndrome that evolves with hypergastrinaemia and hypochlorhydria induced by proton-pump inhibitors (PPIs). This type of induced hypochlorhydria has differences from the one occurring in patients with atrophic gastritis. Under the effect of PPIs, gastric pH undergoes some circadian variations, keeping values below 3.0 at certain times of the day (nadir) as opposed to atrophic gastritis where achlorhydria is permanent. In paediatric practice reduction of acid secretion is frequently induced by the use of H_2 blockers, as ranitidine, or PPIs like omeprazole or lansoprazole. Apart from situations of established acid-induced disease, these drugs are also commonly used in stress situations like extensive burns, complex surgery or intensive care units to prevent ulceration due to increased acid or reduced resistance of the mucosa. In infants, one of the main indications for inducing gastric hypochlorhydria is gastro-oesophageal reflux disease (GERD), although the real benefit of this measure was recently questioned [11].

Autoimmune Gastritis

Autoimmune disease in paediatrics, particularly thyroid disease, Graves' disease or lymphocytic thyroiditis, has been addressed by many studies evaluating the presence of antibodies against parietal cells. Recent papers mention a prevalence of these antibodies in 14–21 % in autoimmune disease [12, 13]. However, autoimmune atrophic gastritis in children is mostly associated with production of autoantibodies secondary to autoimmune disturbance, particularly thyroid disease, diabetes mellitus or coeliac disease. Segni et al. demonstrated that autoimmune gastritis is an early event in children with autoimmune thyroid disease: having evaluated endoscopy in patients with hypergastrinaemia and anti-parietal cell antibodies, it was shown that gastric atrophy was present in 50 % of the subjects [14]. Greenwood et al. reported two cases of autoimmune lymphocytic gastritis as part of polyglandular autoimmune disease with mucosal atrophy, loss of parietal cells, anti-parietal cell antibodies and achlorhydria [15]. In children with autoimmune disease, the presence of anti-parietal cell antibodies and hypergastrinaemia may be early indicators of gastric atrophy and, presumably, hypochlorhydria.

Congenital Genetic Diseases

Mucolipidosis type IV (ML-IV) is a recessive autosomal disease due to the mutation of gene MCOLN1 and one of the congenital causes for constitutional gastric acid deficiency. It is a storage disease where the cellular secretory vesicles fail regeneration pathway ending up included in the lysosome, as lamellar deposits in electronic microscopy. There is progressive/degenerative neurologic disease with amaurosis and loss of

motor competences due to involvement of the white matter, optic nerve and epithelium of the cornea. Various other tissues like the kidney epithelium and pancreatic and hepatobiliary acinar tubes are also affected with typical vacuolisation [16, 17]. In the parietal cell, there may be an inactive ATPase coenzyme protein leading to scarce secretory granules and reduction in the production of hydrochloric acid. Changes observed in the parietal cell resemble those seen in animals treated with omeprazole [18]. In a recent series, 28 patients with ML-IV aged 2–25 years, all had achlorhydria and hypergastrinaemia [19]. In older patients, it was possible to identify atrophic gastritis as well as hyperplasia of enterochromaffin cells (ECC), consistent with long-standing evolution and constitutional nature of the condition.

Gastrectomy in Infancy

Although this is a very rare situation, partial or total surgical resection of the stomach as in gastric primary tumours prevents production of gastric acid and the above-mentioned acidic microenvironment and its benefits.

Watery Diarrhoea, Hypokalaemia and Achlorhydria Syndrome

This syndrome was first described in the 1950s and is characterised by watery diarrhoea, hypokalaemia and achlorhydria (WDHA). We now know that approximately 76 % of cases have hypochlorhydria rather than achlorhydria, and it has been proposed that the condition be renamed as WDHH. In children this syndrome was described in 64 patients occurring between 2 months and 9 years. There is an M:F ratio of 1:1.5 and is generally associated with neurogenic tumours, ganglioneuroma and ganglioneuroblastoma being more frequent, particularly abdominal thoracic or cervical [20–22]. The syndrome is derived from increased secretion of VIP (vasoactive intestinal polypeptide) and sometimes neurotensin (present in the brain and gastrointestinal tract) and other pancreatic polypeptides. However, there are reports of paediatric cases of WDHA without neoplasia as opposed to adults that always have a primary tumour producing VIP [23]. This polypeptide promotes relaxation of the lower oesophageal sphincter, gastric body and antrum and reduction of the production of gastrin and gastric juice with subsequent hypochlorhydria. Exogenous infusion of VIP and synthetic analogues replicates this effect in experimental models. Reversion of the effect has been clinically demonstrated in children after infusion of somatostatin [23]. Any pancreatic primary or secondary neuroendocrine tumour may virtually cause WDHA syndrome that causes intractable diarrhoea in children, dehydration and failure to thrive. Treatment of choice is surgical resection of the primary tumour if present or somatostatin.

Transient Hypergastrinaemia

Achlorhydria resulting from secondary hypergastrinaemia and transient hyperplasia of G cells was described in a child of 23 months of age with fundic gastritis, watery diarrhoea and failure to thrive. Despite normal tests of secretory function in response to pentagastrin, no cause was identified, and it resolved spontaneously 2 years later without further treatment [24].

Consequences of Hypochlorhydria

What may we expect from hypochlorhydria? Which are the main paediatric groups affected by reduction of acid secretion?

Assuming that infection with Hp is very prevalent, is acquired early in life and will continue if not treated, we may certainly classify this as the largest group in terms of achlorhydria in childhood that may evolve into adulthood. Next in terms of frequency are the patients with GERD being treated with PPIs followed by the children and adults with autoimmune disease that may have associated gastritis. There are many publications associating Hp and nutritional, metabolic, immunological consequences following the hypochlorhydric status induced by the infection.

Gastrin regulation of secretion by the parietal cells and its effect in enterochromaffin is regulated by a negative feedback system. Inhibition of secretion leads to a rise in secretin in plasma with

proliferation of enterochromaffin cells, as shown in rats. In humans, proliferation of ECC with production of gastric carcinoids follows a period of sustained hypergastrinaemia (>500 pg/ml) as in atrophic chronic or autoimmune gastritis, but it is unlikely that this process may evolve entirely during childhood [25–28].

As previously mentioned, persistent hypochlorhydria favours the proliferation of bacteria producing nitrous compounds that convert into nitrites and facilitate carcinogenesis of the gastric epithelium. At the same time at neutral pH, ascorbic acid loses stability leading to low intra-gastric levels of vitamin C. This prevents nitrites (derived from ingested nitrates) from transforming into nitric oxide and causes a higher exposure to metaplastic nitric compounds [25, 29]. More than half of patients with common variable immunodeficiency (CVID) have hypochlorhydria and atrophic gastritis, and there have been rare cases of gastric carcinoma in children with this immune disorder [30, 31]. Studies have shown that the concentration of nitrites in the gastric juice of patients with CVID is much higher than those with isolated chronic gastritis [32]. Carcinoma may occur in 5–10 % of these patients which is a prevalence 50 times above the general population, providing support to the mentioned pathophysiology, similar to adults with atrophic gastritis where increased cell turnover favours epithelial metaplasia.

Nutritional Consequences

Malabsorption of vitamin B12 is clearly associated with chronic gastritis and hypochlorhydria. In infancy malnutrition and infection with Hp have parallel incidences, with reciprocal effect [33]. Various paediatric cohorts have shown that Hp infection causes hypochlorhydria of variable magnitude [34–39]. It is also well known that malnutrition favours hypochlorhydria, and this decreases nutrient absorption. In a series throughout the world, a convergence between Hp infection and short stature has been observed, as well as iron-deficiency anaemia and bone mineralisation defects [8, 39–42]. Iron-deficiency anaemia seems to correlate directly with Hp infection in areas where oral intake of iron seems adequate in the absence of prevalent intestinal parasitic infections (this factor induces important bias studies in developing countries) [39]. Hp infection causes hypochlorhydria and decreases iron absorption as mentioned above, leading to iron deficiency. In three cases correction of iron deficiency was only achieved after eradication of Hp [43]. The absorption of folic acid is also compromised due to a rise in pH partly because vitamin C is less stable [44].

Vitamin A is formed from its precursor β-carotene in ingested food. Bioavailability depends on several factors, namely, ingestion of fresh foods. Tang et al. have sown that hypochlorhydria and achlorhydria affect and reduce its bioavailability [45].

Hypocalcaemia and Hp infection were identified in clinical studies in adults. The rate of hip fracture and osteoporosis correlated with the prolonged use of PPIs, and this seems to provide additional evidence relating to reduced calcium absorption and decreased acid secretion [46, 47].

Infectious Consequences

Hypochlorhydria reduces the potent natural antibacterial filter and may favour bacterial proliferation not only within the stomach but throughout the gastrointestinal tract [48, 49]. In vitro studies using chemical simulation of gastric juice have demonstrated that gastric juice has a bactericidal effect over *E. coli* O157:H7, which is a rather frequent agent in paediatric practice [50]. Elevation of gastric pH may be an important facilitator of infection in humans through agents like *Vibrio cholerae*, *Campylobacter jejuni*, *Giardia lamblia*, *Serratia* and several strains of *Salmonella* [1, 2, 39, 51, 52]. In a study among children from Peru, the presence of cholera was significantly associated with infection with Hp in children below 10 years of age in Peru, and the presence of Hp was the sole independent factor even correcting for low social and sanitary conditions [53]. In the same series, the use of antacids was not associated with cholera, and this may correspond to better health care and access to potable water.

In a hospital setting, there was an increased risk of diarrhoea by *Clostridium difficile* among

inpatients after intake of PPIs, and other recent series report a higher incidence of pneumonia in this subgroup of patients [54–56]. For a long time, there has been a perception that immunocompromised patients being treated with inhibitors of acid secretion are more prone to infection, especially in adults. The increased risk of nosocomial infections among patients in intensive care units taking PPIs was recently taken into ambulatory setting: it was also observed that patients without co-morbidities taking antisecretory drugs also had an increased risk for pneumonia. However, paediatric studies on this issue are very rare. The use of omeprazole in preterm newborns has been associated with an increased risk of necrotizing enterocolitis and potential systemic infections [57]. Naturally these complex patients have a number of other factors in intensive neonatal units that need separate assessment besides hypochlorhydria and changes in the intestinal microbiota.

An interesting study was performed by Canani et al. in a paediatric population on chronic treatment with PPIs for GERD [58]. A significant increase in the incidence of pneumonia and gastroenteritis in the treatment group was observed, and hypochlorhydria was the independent risk factor; however, this was a small study group. Additional paediatric studies are needed because empirical anti-secretory treatment is widely prescribed for long periods in small infants hoping to abolish signs and symptoms presumably associated with GERD. However, there is some evidence that the symptoms usually associated with GERD not only persist but also seem to have little relation with PPI intake and reduction of acid secretion, raising the hypothesis that non-acid reflux may contribute to the clinical picture that prompts for therapy [11]. Strict selection of high-risk patients for treatment with PPIs may minimise the above-mentioned complications.

Immunological Consequences

Protein digestion started in the stomach has benefits beyond nutrition. Hydrolysis of proteins may have immune consequences that were unknown until recently. Identification of adults with chronic gastritis developing de novo immunogenicity to alimentary antigens that were previously tolerated prompted for research in this area. Reduction of proteolysis adds an allergenic potential to ingested proteins. Mechanisms of alimentary intolerance, especially IgE mediated, are mainly related to the size of macromolecules presented to the intestinal mucosa, although we know that some intact proteins may be found in the small intestine and even in the bloodstream [59]. It is possible to simulate gastric juice in vitro in a way to promote proteolysis of food fragments that would otherwise be allergenic [60]. If pH rises in this controlled setting, this hydrolytic capacity is compromised, thereby increasing sensitising risk. The same experiment was simulated in experimental animal models after injection of omeprazole [61]. Untersmayr et al. have demonstrated that the lack of proteolytic potential increases in patients under treatment to inhibit gastric secretion along with increased de novo production of IgE [62]. Perception that gastric hypoacidity may be the first obstacle to modulation of food tolerance has a prominent role in paediatrics as the incidence of alimentary allergy is twice that found in adults given the increase in tolerance with age. In this context prevention of situations that evolve with hypochlorhydria *may* play an important role in prevention of food allergy.

Conclusion

Hypochlorhydria in infancy and childhood seems to be a far more common phenomenon than usually recognised. If we associate infection with Hp to transient achlorhydria and chronic gastritis, we may realise that a substantial number of older children, adolescents and adults may have a considerable reduction of acid secretion. In small infants there is a subgroup with feeding or swallowing difficulties to which PPIs are often prescribed empirically, assuming that there is GERD. Prescription of PPIs in children became as common as antipyretics in some communities.

Consequences of reducing acid secretion may be deleterious or even outgrow potential benefits. Among those there is reduced absorption of iron, calcium and vitamins as well as exposure to ingested bacteria increasing the

risk of infection (not only gastrointestinal). The role of allergenic sensitisation, although paediatric studies are lacking, may also be considered. Finally, there may be a small increase in the risk of malignancy that may evolve slowly from child to adulthood although very rare in children.

Medically induced hypochlorhydria especially for prolonged periods should only be undertaken after clear analysis of benefits versus potential risks. Further paediatric studies may shed additional light into this discussion.

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Gastric Bleeding and Perforation 122

Jürgen Schleef

Introduction

Gastric bleeding and perforation are rare events in children. Upper GI pathology represents only about 20 % of all episodes of intestinal bleeding or perforation [1]. The clinical appearance is often more severe and acute than in the lower GI tract. Both bleeding and perforation of the stomach might occur in all age groups ranging from preterm patients to adolescents. Aetiology and cause of bleeding and perforation differ significantly from age to age. Causes can be iatrogenic (tube, probe, medical therapy), malformative (vascular malformation, stenosis, atresia) and acquired (tumorous, secondary to infections and hepatic disease). In all cases, a precise history, a clinical workup and a diagnostic approach should be performed. In acute cases, intensive care therapy and support should be the first step to ensure vital parameters and stable conditions for further investigations and therapeutic measures. Diagnostics should in all cases include a laboratory workup, radiological investigations and, if possible, endoscopy. A surgical exploration for diagnostic purposes can be necessary in rare situations. If general conditions are stable, a diagnostic laparoscopic approach might be the first choice.

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Gastric Bleeding

Gastric bleeding forms an important part of upper GI bleeding. Usually this represents an emergency and needs in all cases immediate further investigation. Clinical gastric bleeding is usually a blood loss from the upper GI tract (haematemesis). The source of the bleeding can be elsewhere in the oropharynx, oesophagus, stomach or duodenum. It can be continuous, intermittent, acute or chronic. Therefore it is difficult to divide a clinical upper GI bleeding into locations, but it can be classified according to age groups as described by others [2, 3] (Table 122.1).

How to Approach a Paediatric Patient with Upper GI (Gastric Bleeding)?

As mentioned briefly, upper GI or gastric bleeding is not frequent in children. Nevertheless, it is always considered a severe condition, even if it is not serious at all in some situations (swallowed maternal blood).

Therefore, a precise history is extremely important in order to get information about the location of the bleeding. The patient's age is the most important fact, since especially in early life (the first days) of a healthy child, vomiting of ingested blood is the most frequent condition, which does not affect the patient at all, if there is no risk of aspiration of maternal blood [4]. A thorough exam of the oropharynx is important to

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Table 122.1 Causes of gastric bleeding according to the age of the patient

Neonates	<2 years	>2 years
Swallowed maternal blood	Oesophagitis/gastritis	Oesophageal/gastric varices in portal hypertension (hepatic disease, post-op, biliary disease, portal thrombosis)
Haemorrhagic disorders of the newborn	Gastric ulcer	Gastric ulcers
Vitamin K deficiency	NSAID/drug-induced ulcer disease	Vascular malformations
Acute gastritis (stress, post-op, NICU patients)	Foreign body ingestion (e.g. batteries)	Bleeding induced by vomiting (Mallory–Weiss, Dieulafoy)
Gastroduodenal malformations (web, stenosis)	Vascular malformations	Bleeding from tumorous lesions
Maternal drugs	Swallowed blood from the naso-/oropharynx	Bleeding from gastrostomy sites
	Bleeding from gastrostomy sites	

exclude a bleeding with subsequent swallowing of blood mimicking a gastric bleeding. Sometimes small mucosal tears after repeated tube insertions can become a source of bleeding. The general conditions (other underlying problems like organ dysfunction and bleeding disorders) might not be already well studied and known. Red blood vomiting can be related to a stress situation with stress ulcers. Stress (NICU patients or patients being operated as a newborn) should always be considered as a risk factor. The general condition of the child at the time of bleeding is important since fever might indicate an infectious condition of an underlying disease. The history of the mother should always be known, since some kind of maternal medication (NSAID) or drug abuse can cause bleeding in the newborn. In newborns a history of continuous vomiting since birth might be a hint to a malformative condition at the level of the stomach outlet (web, pyloric stenosis) that can be the cause of bleeding [5].

In the elder group of children up to 2 years, the history should focus more on general medical conditions. Especially liver dysfunction (history of jaundice, previous surgery of biliary disease) can be an underlying condition for gastric bleeding from varices. The most frequent cause in this age group is oesophagitis and gastritis. Oesophagitis is probably the most common cause of upper GI bleeding and cannot be distinguished clinically from a gastric bleeding. The history of these children is often typical (regurgitation, dysphagia and failure to thrive). Many of these patients are syndromic or handicapped children. Drug therapy (NSAID, cortisone) can be another cause of bleeding. In some cases a history of foreign body ingestions should be evaluated, since swallowed batteries and cleaning tabs might cause local necrosis and severe damage to the mucosa. In some instances this can also lead to organ perforation and vascular damage.

In the elder groups of children and adolescents, causes are very similar. In this group general underlying conditions and diseases are usually well known, but the general conditions due to chronic organ failure are often not good and can be critical. For adolescents another typical and frequent condition can be due to recurrent vomiting, a Mallory–Weiss or Dieulafoy lesion of the stomach mucosa. Sometimes this can be due to acute alcohol intoxication or incidental drug abuse. In rare instances a gastric tumour in adolescents can be the cause of a gastric bleeding. This could be a lymphoma or a, in rare situations, a primary gastric cancer.

Physical Exam

The initial and quick physical exam of the patient is very important. In all patients with bleeding, you should look for signs of shock (skin colour, heart rate, blood pressure and capillary refill, grade of consciousness). The examination of the heart, nose and throat should be concentrated on erosions from caustics, oropharyngeal mucosal

erosions or lesions, fresh blood and clotted blood in the nose and throat. The thorax and abdomen should be inspected for scars or abnormal superficial vessels/caput medusa, which indicate previous surgery and portal vein occlusion (oesophageal atresia and reflux disease, biliary atresia and secondary liver disease). The palpation of the abdomen might indicate an enlarged liver or spleen as a clinical sign of hepatic disease or portal hypertension. Hyperperistalsis might be present in upper GI bleeding. If the abdomen is tender with a peritoneal irritation, a perforation might be considered. The evaluation of consistence and colour of the stool can be important. A serious gastric bleeding might lead to the loss of red and fresh blood through the anus, while black stool might be a sign of a more chronic upper GI bleeding [5].

Instrumental Examination

As mentioned before, the most common cause of upper GI bleeding in neonates is due to the ingestion of maternal blood. To avoid expensive and unnecessary exams, a simple Apt test can be performed to differentiate between maternal and foetal blood. By mixing the blood, aspirated from the gastric tube, with 1 % of sodium hydroxide, maternal blood will result in a brown-yellowish colour, while foetal blood (haemoglobin) will give a bright red colour. If this test confirms maternal blood in the stomach of the newborn, no further investigation is necessary.

The diagnostic in all other cases with upper GI/gastric bleeding is usually based on radiological exams and endoscopy. The first exam is a plain x-ray of the thorax and abdomen to rule out free abdominal air or pneumomediastinum. The next step is an ultrasound exam of the abdomen. Hepatic disease is often expressed with liver enlargement and portal hypertension as well as splenomegaly. A Doppler exam of the portal and hepatic vessels can be helpful to verify the presence of enlarged portal vessels, splenomegaly and pathological blood flow and direction. Abdominal masses, like lymphomas or tumours, can be recognized.

The most important diagnostic tool is usually an upper GI endoscopy. Under direct vision the mucosa of the oesophagus and stomach can be controlled, and eventual bleeding sources can be visualized. This exam can be difficult in patients with severe massive bleeding due to the lack of vision. Intensive cleaning of the gastric cavity with large amounts of cold water can usually resolve this problem. Endoscopy is not only diagnostic but can be combined with therapeutic manoeuvres under direct vision like sclerotherapy, clipping or coagulation of bleeding vessels or ligation of varices. In rare situations, where the source of bleeding cannot be clearly defined, further investigations might be necessary. These can be an angio-CT scan and sometimes also an angiography to verify vascular malformations. In very small children (preterm and newborns), these techniques might not be applicable since these children are very often too unstable for being transported. In these cases a symptomatic/medical therapy and some kind of bedside exam (plain x-ray, ultrasound and endoscopy) are the bases for the diagnosis.

Therapy

The treatment of gastric bleeding in all cases and age groups is based on a symptomatic and supportive approach and a specific treatment of the bleeding itself. The first approach consists of IV fluid infusion and stabilization of the circulation and vital parameters. Once the blood loss can be estimated, a blood transfusion and substitution of clotting and coagulation factor should be undertaken [6]. In stable condition further diagnostic should be performed. As mentioned above the most important exam is an endoscopy. If bleeding from the stomach is verified, different options could be selected.

In newborns, being on NICU care, the most frequent cause would be stress gastritis. In these cases, once the diagnosis is made by endoscopy, a treatment with omeprazole should start (2 mg/kg IV/day). This can be combined with ranitidine (1 mg/kg IV 4/day). If the child is too small or too unstable for endoscopic diagnostics, the

treatment should be started in any case. To treat a possible vitamin K deficiency, 1 mg of vitamin K IV should be administered. If the bleeding does not stop within 2 h, fresh frozen plasma has to be given. About 0.25–0.5 % of newborns present this deficiency causing bleeding in the first days of life. Once the bleeding is stopped, further investigation should be performed to rule out rare causes and malformations.

In the group of children in the first year of life, the most frequent causes of bleeding are reflux disease and oesophagitis. After endoscopy the treatment should be medicated with omeprazole and ranitidine. After the acute phase, children should receive a prophylactic therapy and further investigation. If a gastritis is present and resistant to the initial therapy, a *Helicobacter* infection should be ruled out [7]. Sometimes in this age group, also off-label therapies with NSAIDs can cause a bleeding. Finally, very rarely also Crohn's disease can be observed in the first year of life. Therefore biopsies should always be part of the initial endoscopic diagnostic.

In all other children, the most frequent cause is again diffuse peptic ulcer disease, very often correlated to *Helicobacter* infections. If the endoscopy confirms a single bleeding source (mucosal vessel), an endoscopic sclerotherapy or clipping or coagulation is the treatment of choice. If varices are identified, they should be ligated or clipped in the acute situation. A control endoscopy is always necessary to review the result of the initial treatment and to proceed with a prophylactic treatment. Naturally the further diagnostic should include an evaluation of the hepatic function and a possible associated portal hypertension. In these cases octreotide can be used. The dose suggested in the literature is 1 mcg/kg IV as an initial bolus followed by a continuous IV application (1 mcg/kg IV/h). The treatment has to continue 24 h after the bleeding has stopped and will then be reduced stepwise. This therapy is also an off-label therapy in children. Another therapeutic approach is by the application (off label) of vasopressin. The starting dose in the literature for children is 0.002–0.005 U/kg IV/min. The total doses should not be higher than 0.01 U/kg IV/min. The therapy continues 12 h after the bleeding has stopped and is consequently reduced within 48 h to zero. Recently in the literature, a therapy with a high-dose application of propranolol lowering the portal pressure is described as a chronic treatment strategy in these children. The doses are similar to the treatment in adult patients but should be adjusted under controlled hospital conditions individually [8].

A small group of patients will present with vascular malformations, causing bleeding from the stomach wall. In this case a precise diagnostic should be performed and, if possible, a sclerotherapy is the best therapeutic choice. Only in very rare situations, a surgical resection or ligation of vessels might be necessary [9].

In children presenting with gastric tumorous disease, the treatment of the bleeding should be symptomatic, followed by a specific oncologic therapy. There are rare cases where a surgical resection remains the only choice to resolve the bleeding.

Some children present following the ingestion of dishwasher agents or other cleaning products. Usually these cases do not show a severe bleeding and should be treated according to well-established protocols. Ingested foreign bodies, which might cause mucosal necrosis and subsequent bleeding and perforation (batteries), should be removed as soon as possible [10].

Conclusion

Gastric bleeding in children is rare. The approach is well standardized and orientated according to the age, the general condition of the child and other underlying disease. In the literature the incidents are not clear, but it should be a rare event. Mortality rates are not known, but in some cases children might die during the acute phase. Nevertheless, mostly the general condition and the presence of systemic (coagulopathies) or organic (portal hypertension and liver failure, malignant disease) diseases are conditioning the prognosis of the patient. Many conditions, leading to an acute event, can be prevented by prophylactic medical treatment (omeprazole and ranitidine) and control of portal hypertension and varicose

disease (Rex shunt, sclerotherapy or banding of varices, systemic propranolol treatment).

Gastric Perforation

A perforation of the stomach is a rare event in children and represents usually an acute and dramatic situation for the patient. Most of these cases do present with a "free perforation" into the abdominal cavity (pneumoperitoneum) and acute enlargement of the abdomen. The frequency of this event is not well known. It can appear in any age group, and the aetiology can be spontaneous or associated to inflammatory, tumorous and malformative conditions. Perforation can be further a complication of diagnostic (endoscopy with biopsies) or therapeutic procedures (dilatation, laser coagulation) or placement of NG tubes. Special entities are patients with complications and perforation associated with gastrostomies.

Diagnostics

As mentioned before gastric perforation is usually associated with an acute event and dilatation of the abdomen. The patient often presents with a shock situation and respiratory failure, especially in newborns. In a small group of patients with non-acute symptoms, the diagnosis of gastric perforation can be difficult. Generally in all patients after gastric surgery and tube placements with consecutive signs of an "acute abdomen", a gastric perforation should be suspected. The most important and usual first exam in these patients is an abdominal x-ray. Usually a pneumoperitoneum can be detected. If the location of the perforation seems to be unclear, a contrast study via an NG tube or a gastrostomy tube can be performed. A CT scan might be helpful to understand the anatomical relationship between the stomach wall and other organ structures. In unclear cases an endoscopy can be performed to understand the cause of a suspected perforation or lesion. This can be in some instances a tumour or inflammation.

Neonatal Gastric Perforation

In newborns a gastric perforation presents with increasing tenderness of the abdomen, which becomes increasingly irritated, associated by emesis and bilious gastric juice. It is important to detect this event as early as possible to avoid a septic shock and peritonitis in these small children followed by anuria and respiratory failure. The abdominal distension is worsening and compromising the respiratory situation. The most important exam is a plain x-ray of the abdomen [11].

In case of a pneumoperitoneum, a nasogastric tube should be placed, and the child should be prepared (resuscitation) for surgery as soon as possible. In some cases this should be performed in a NICU setting to avoid unnecessary transportation of the unstable and fragile patient. An upper abdominal laparotomy is performed and the gastric perforation identified. A limited debridement of the area of the perforation should be performed. The tissue borders should be viable and well perfused. The defect should be closed by a double-layer suture avoiding a stenosis or extensive resection of the stomach tissue. In all cases a complete inspection of the stomach is necessary to avoid the overseeing of a second perforation. This might occur in case of an anterior disruption due to a tube or probe placement, where the tear can also involve the posterior wall. Some authors use the omentum to cover the suture site. We do not perform a post-op drainage of the abdominal cavity in this case but only a lavage of the abdomen. An intra-gastric tube is left in place for decompression of the stomach. The post-op treatment consists of a broadband antibiotic therapy and intensive care support. Post-op mask ventilation with positive pressure should be strictly avoided. The factors, contributing to the prognosis of these children, are the grade of prematurity and associated problems, the length of the interval between the perforation and the detection, the extension of a possible peritonitis and the grade of respiratory complications. In this group of children, the mortality rate is around 50 % according to the literature.

The aetiology of this pathology is not clear in most cases [12]. Three aspects are usually

described and proposed: trauma, ischaemia and spontaneous perforation. The vast majority of these instances are due to iatrogenic trauma by tube placement. Another cause is an overdistension during positive-pressure ventilation especially by mask ventilation. Spontaneous perforations of the stomach have been observed within the first week of life. In these cases no specific clinical event or trauma can be identified besides prematurity and perinatal stress. Of all cases spontaneous perforation occurs in about 20%. Some authors describe a congenital defect with the absence of a part of the gastric muscle layers predisposing as a reason for perforation. A further possible cause is a distal obstruction in some cases (duodenal stenosis, duodenal web, jejunal stenosis). A recent retrospective study from Japan reports an incidence of 8.8% of 16,556 NICU which underwent surgery, but only 0.76% account for gastric perforation. The authors report in their survey a mortality rate of 36% over a 20-year period [12].

Factors affecting a negative outcome are in all major studies the delayed diagnosis, prematurity, acidosis and respiratory failure and peritonitis at the time of surgery. Some single reports do exist emphasizing a successful non-surgical treatment (drainage) of gastric perforation. No bigger series exist and experiences are too small and limited to give any further recommendation. This technique might be like in other intestinal perforations in newborns an alternative approach in the unstable and non-operable patient.

A particular situation can be seen in NICU patients with intratracheal high-pressure ventilation. An alveolar rupture might cause a pneumomediastinum and subsequent pneumoperitoneum mimicking a gastrointestinal perforation. This situation is usually unclear and might need an exploratory laparotomy (Fig. 122.1).

A rare cause for perforation might be a volvulus of the stomach, causing ischaemia and perforation (Fig. 122.2).

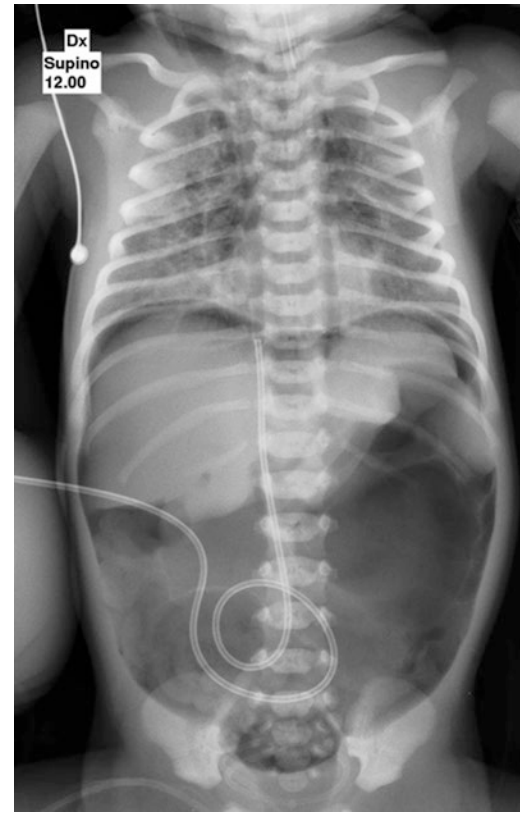

Fig. 122.1 X-ray study: preterm baby with pneumoperitoneum after high-pressure ventilation. The laparotomy excluded a perforation of the viscera

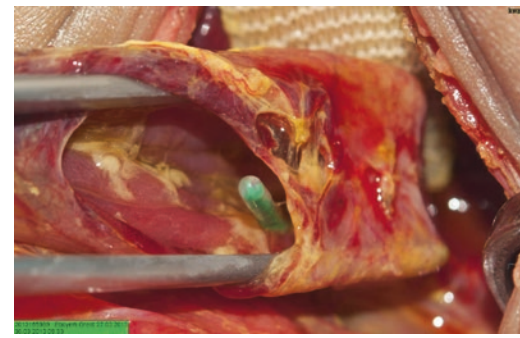

Fig. 122.2 Major perforation of the stomach at the larger curvature due to perinatal gastric volvulus (Case from Prof. Till, Graz, Austria)

Gastric Perforation in Elder Children

In elder children gastric perforation is a very rare event. It is mostly traumatic, iatrogenic and in rare cases due to an ulcer disease of the stomach. A bigger group of children with perforation of the stomach are belonging to children having complications of gastrostomy tube insertion or changing of gastrostomy buttons. It seems to be that gastric perforations due to trauma occur more frequently after meals and gastric dilatation. Usually this

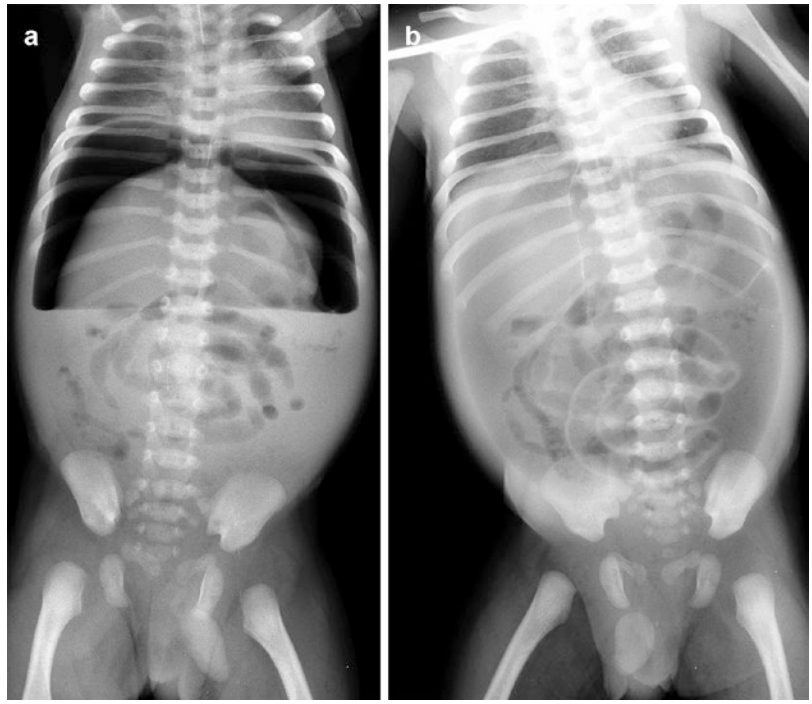

Fig. 122.3 "Battered child" (4-month-old boy) with gastric perforation (x-ray with massive pneumoperitoneum; (**a**) erect x-ray and (**b**) supine)

finding is associated with a blunt abdominal trauma and represents only 0.9–1.8 % of all abdominal traumas. The trauma can be due to an accident but also to a "battered child" syndrome. In all cases the clinical signs are the acute distension of the abdomen, pneumoperitoneum on abdominal x-rays and respiratory distress (Fig. 122.3). All these patients need a surgical exploration of the abdominal cavity, and further investigations are usually a loss of time. The therapeutic measures before surgery (resuscitation, broadband antibiotic therapy) were already mentioned before. In case of a suspicious trauma, caused by an accident or a second person, a thorough photographic documentation should be performed for further legal considerations. The site of rupture or perforation can be elsewhere but is more often described at the anterior part of the stomach wall. Therapy should include the excision of wound edges, lavage of the cavity and closure of the stomach, which need for some days an intraluminal decompression and drainage. The mortality rate in this group is lower than in the newborn population but determined by secondary injuries during trauma. A very important critical aspect is delayed diagnosis due to necrosis of the stomach wall and general peritonitis, causes by the spillage of gastric juice into the peritoneal cavity [13].

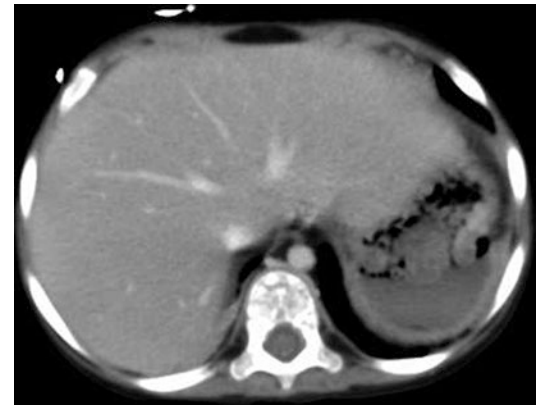

Fig. 122.4 CT scan of the upper abdomen. Two-year-old girl with ALL and massive systemic aspergillosis. The aspergilloma perforated from the spleen into the stomach. The child was admitted with gastric bleeding and during the gastroscopy, the perforation was detected

Infectious or tumorous lesions from adjacent organs can be responsible for a gastric perforation (Fig. 122.4). In these cases a CT scan or a study with water-soluble contrast media might be helpful to get the diagnosis.

Gastric Perforation Associated to Gastrostomies

Gastrostomies can be inserted by endoscopy (PEG), laparoscopy or laparotomy. One of the associated risks is a gastric perforation, in some cases overseen at the time of surgery. These perforations might happen during the blind puncture of the stomach during an endoscopy, causing a perforation and consecutive fistula between the stomach and other hollow organs (colon, small bowel). Sometimes the puncture can cause a laceration at the posterior part of the stomach (dorsal stomach wall), with a consecutive extravasation of gastric juice. This laceration might be overseen during the endoscopic gastrostomy placement. In some instances the gastrostomy tube is removed and substituted by a gastrostomy button without endoscopic control. In this case, even months after the PEG placement, the dilatation of the balloon outside the stomach wall can create a dehiscence of the stomach from the anterior wall and a consecutive fistula of the stomach into the abdominal cavity. If this problem is observed during an endoscopy, a new gastrostomy (PEG) catheter can be inserted, fixing the stomach again to the anterior abdominal wall, without major harm to the patient. If this problem is not recognized early, a peritonitis and pneumoperitoneum might occur later, presenting a patient in a serious clinical condition [14].

But even a laparoscopic assisted or open gastrostomy placement can cause later problems and gastric perforation. A gastrostomy constructed under tension might detach from the anterior abdominal wall and create a "free" intraperitoneal perforation. Sometimes traction sutures are used to fix the stomach in its position. If these traction sutures were tired due to too much traction, they could consecutively cut the stomach wall and create leakage of gastric juice (Fig. 122.5). In these patients, a peritoneal reaction and abdominal tension associated with vomiting might be the first clinical signs.

In all situations with a doubtful gastric perforation or leakage, a contrast study via the gastrostomy tube should be performed to rule out any extravasation of contrast media into the abdominal cavity. There are no clear numbers but some authors describe a rate of up to 2 % of perforation during or after gastrostomy placement.

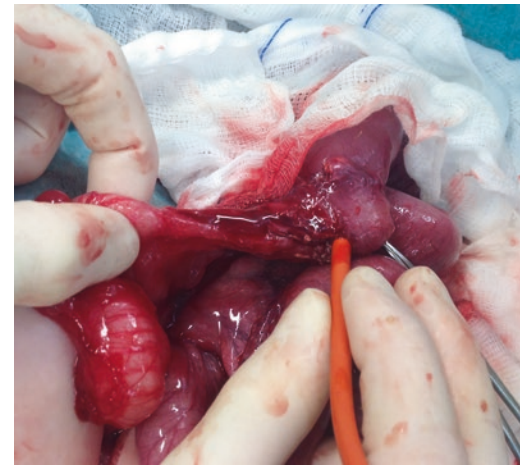

Fig. 122.5 Five days after PEG insertion with push technique and T-bar fixation of the stomach. The T-bars "migrated" through the wall of the stomach and caused a gastric perforation with leakage of gastric juice into the abdomen

Conclusion

There is a high variety of causes and complications leading to gastric perforation in any age group. For the newborn group, some typical clinical situations might occur, while in the elder group, gastric perforation is very rare. For all groups and situations, some rules concerning diagnostic and therapeutic procedures can be established.

Manipulation with probes and tubes in the stomach and consecutive abdominal distensions and abdominal resistance should lead to diagnostic ruling out of the stomach perforation. Abdominal trauma and consecutive abdominal distension are clinical situations suspicious for a hollow organ perforation. If a pneumoperitoneum is detected, stomach perforation should be ruled out. The prognostic factors in all patients are the general conditions of the child and the presence of a peritonitis and sepsis.

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Ménétrier's Disease

123

Ann Matthai

This is a rare acquired disorder of the stomach characterized by hyperplastic folds in the gastric fundus and body. It is a protein-losing gastropathy [1] resulting in hypoalbuminemia and accompanied by increased mucous secretion and hypochlorhydria. This was first described by a French pathologist Pierre Eugene Ménétrier in 1888 who noted hyperplastic changes in the gastric mucosa of some cadavers. Ménétrier's disease is seen in adults and children. Unlike pediatric disease, that in adults is progressive and more often associated with *Helicobacter pylori.*

Etiology and Pathogenesis

There have been many case reports of Ménétrier's disease in children associated with CMV infection. In one series coinfection with *H. pylori* was noted in one case. Recently Sheffield Children's Hospital had a case associated with swine flu.

The exact pathogenesis is not clear but pioneering work has been done by Coffey et al. in identifying the role of transforming growth factor alpha (TGFα) and epidermal growth factor receptor (EGFR) [2, 3].

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Transforming growth factor alpha (TGFα) is a 5.6 kd single-chain polypeptide that acts through binding to the epidermal growth factor receptor (EGFR). TGFα is produced in a wide range of normal as well as embryonic and neoplastic cells and tissues. TGFα and EGFR, but not EGF, are expressed in normal gastric mucosa. TGFα has a gastroprotective role, namely, inhibition of acid secretion and stimulation of mucous cell growth.

The normal oxyntic gland in the gastric mucosa has progenitor cells which give rise to surface mucous cells, parietal cells, chief cells, and neuroendocrine cells. In Ménétrier's disease there is expansion of the surface mucous cell compartment at the expense of parietal and chief cells. It is hypothesized that these changes are due to increased signaling of the epidermal growth factor receptor by TGFα. TGFα immunostaining in the gastric mucosa of four patients with Ménétrier's disease showed that in contrast to the normal pattern of TGFα immunostaining, in which TGFα appears most concentrated in parietal cells, there was intense staining in the majority of mucous cells. Transgenic mice, which overexpress TGFα in the gastric mucosa, exhibit a number of features characteristic of and consistent with the diagnosis of Ménétrier's disease, including foveolar hyperplasia and glandular cystic dilatation.

The most common symptoms are vomiting, abdominal pain, and edema. Anemia may be seen due to gastric blood loss, or reduced absorption

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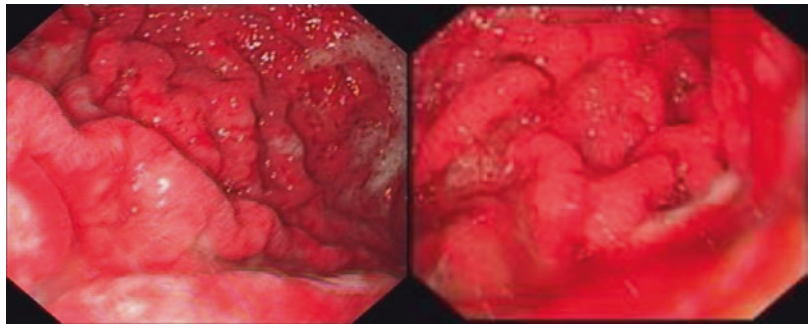

Fig. 123.1 Courtesy Department of Gastroenterology, Sheffield Children's Hospital

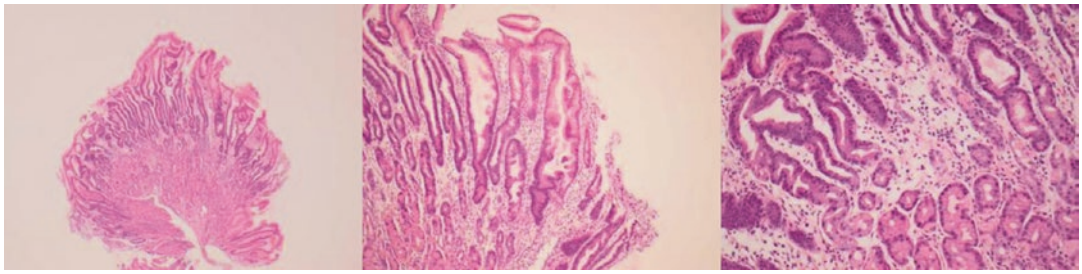

Fig. 123.2 The gastric mucosa with elongated hyperplastic crypts and focal cyst formation

of iron due to hypochlorhydria. Weight loss has also been noted.

The diagnosis is established by upper GI endoscopy which reveals giant gastric folds (Fig. 123.1), and histology demonstrates foveolar hyperplasia (expansion of mucous cells) and cystic dilatation of glands (Fig. 123.2). Ultrasound can detect hypertrophic gastric folds and point toward the diagnosis. Differential diagnosis includes Zollinger-Ellison syndrome where there is hyperplastic gastric folds but with high gastrin levels and hyperchlorhydria.

Treatment

Most cases in children need only supportive treatment and albumin infusions.

Omeprazole has been used in adults but it is not clear whether *H. pylori* eradication was more effective. Somatostatin analogue octreotide has been used successfully in children [4]. Eradication of *H. pylori* and treatment of CMV with ganciclovir have also resulted in resolution of long-standing disease in children [5]. Recently monoclonal antibody to EGF receptor has been tried successfully in adults [6, 7].

Prognosis in children is good as it is not progressive, and chronic cases have responded to treatment of underlying cause.

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Inflammatory Bowel Disease and the Stomach

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Robert Heuschkel

Introduction

Crohn's disease (CD) is known to occur in any part of the gastrointestinal (GI) tract, although it is the terminal ileum that was the site that initially identified the disease as a distinct clinical entity [1]. Similarly ulcerative colitis (UC) has traditionally been considered to involve only the large intestine, although the so-called backwash ileitis is a recognised feature of more extensive UC. The increasing reliance on endoscopic appearance and ability to develop tissue-based diagnostic algorithm has inevitably blurred the boundaries between apparently distinct clinical entities.

Gastroduodenal involvement in IBD was initially recognised in the late 1940s [2]; however the inflammatory changes in the upper GI tract have only recently been more formally documented [3–6].

The classical anatomical distributions of CD and UC suggest that study of the upper GI tract by endoscopic and histological techniques can help differentiate the two conditions. The presence of inflammation in the stomach does not however confirm a diagnosis of CD, as a number of researchers have reported upper GI tract changes in patients with UC [7–10]. Upper GI involvement remains more common in CD than UC [9]. The increasingly common diagnosis of indeterminate colitis (IC) – now known as IBD – unclassified (IBD-U) – is largely based on the increase in diagnostic oesophago-gastroduodenoscopies (OGDs), at which routine biopsies are now more frequently taken. Additional findings in the upper GI tract have surely provided more clinical information; however they have also complicated a previously straightforward classification. A diagnostic OGD is now strongly advocated in addition to an ileocolonoscopy [3, 6, 11, 12].

The ESPGHAN IBD working group recommended that all children suspected of having an inflammatory bowel disease should undergo upper GI endoscopy and colonoscopy with ileal intubation [11]. Radiological imaging of the small bowel has also been recommended in all cases except in definite UC.

The hard data remains limited, with the definitions of upper GI 'involvement' not being consistent. Varied terminology for endoscopic appearances of the gastric mucosa is used, and in some studies it is not made clear whether abnormalities refer to endoscopic or histological anomalies. In the absence of clear descriptive endoscopic terminology, retrospective studies suffer terribly from individual reporting bias. This may gradually be improving as standardised reporting tools are becoming more widely used.

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Incidence and Epidemiology

The overall incidence of IBD in childhood is increasing in the paediatric age group [13].

A two-phase, 7-year retrospective study showed abnormalities on OGD in 64 % of children with CD and 50 % with UC; histological abnormalities were found in 81.6 % and 70.6 % of these cases, respectively [14]. Castellaneta et al. showed that upper GI inflammation was evident in 29/65 children with suspected IBD included in their study, of these 81.4 % had CD and the remainder had UC. They reported that inflammatory changes were most common in the stomach followed by the oesophagus and then duodenum [6].

In UC, as in CD, the stomach is most commonly affected within the upper GI tract [8, 9, 14].

Another retrospective study involving 196 children with Crohn's disease, only 25 children underwent an OGD for symptoms of upper GI involvement. Overall the group reported an incidence of upper GI abnormalities in only 5.1 %, with a male predominance of 8:2 [15]. The incidence of upper GI involvement was 40 % in the symptomatic group (10/25).

It appears there is a greater risk of having upper GI involvement in CD if a child has both small and large bowel disease (33 %, $p<0.05$). In a 15-year retrospective study involving 230 children with CD, with average follow-up of 6.6 years, 69 (30 %) had endoscopic upper GI involvement. There was no significant difference between sexes [4].

Clinical Features

The most common upper GI symptoms in Crohn's disease are epigastric pain (65 %), vomiting and weight loss [15], although dysphagia, aphthoid ulcers and pain on eating have also been reported [4]. It also appears that weight loss and hypoalbuminaemia are overrepresented in this group of patients. It is worth remembering that between 19 % (13 of 69) children with abnormalities did not exhibit any upper GI symptoms in this series and that others also report that there is no clear correlation between the severity of clinical symptoms and upper GI involvement [9].

Although gastroduodenal obstruction is a potential complication of persistent upper GI inflammation, none of the patients included in these studies had this complication during their relatively short follow-up period. Significant upper GI bleeding is even less common [15], but can be extremely severe and require emergency endoscopic intervention.

In their 2-year prospective study, Castellaneta et al. showed upper GI involvement was significantly higher in children with ileocolonic involvement compared to those with ileal or colonic involvement alone (71 % versus 36 %; $p<0.05$) [6]. Clinical symptoms suggestive of upper GI tract involvement were found in 56 % of 54 children included in this study. Of the symptomatic group, 33 % did not have inflammation of the upper GI tract. The common presenting symptoms recorded for children with upper GI involvement were epigastric pain, abdominal pain, nausea and/or vomiting and weight loss. Although these symptoms were significantly more common in children with upper GI involvement, in this series there was no significant correlation between low albumin levels or mouth ulcers and upper GI involvement in this cohort.

In another prospective study involving 31 children with CD, the authors reported that only 16 % had symptoms suggestive of upper GI involvement, 42 % had endoscopic findings, whilst there were histological changes in 87 % (granulomas in 39 % and nonspecific inflammatory changes in 48 %) [3]. This group concluded that there was no correlation between clinical, radiological and histological data.

Children with Crohn's disease and focally enhanced gastritis (FEG – see below) are more likely to have upper GI symptoms as compared to those without; however none of the children with FEG in UC had symptoms to suggest upper GI disease. GI symptoms alone did not indicate the presence of FEG in children with IBD [12].

Endoscopy

When IBD is confined to the colon, conventional colonoscopic and histological criteria alone may fail to establish a definitive diagnosis, and hence it is increasingly recommended, at least at diagnosis, to perform an OGD with biopsies.

The Porto criteria developed by the IBD working group of ESPGHAN strongly advocate upper endoscopy in all children with suspected IBD, irrespective of the presence or absence of upper intestinal symptoms. Not only does this provide potential diagnostic clues, but it also allows the detection of pathology. During upper GI endoscopy, biopsy samples must be obtained from inflamed and non-inflamed gastric mucosa to maximise diagnostic benefit [11].

Upper GI endoscopy may be helpful in distinguishing between CD and UC, even in patients who do not have symptoms suggestive of proximal gastrointestinal involvement [3, 4].

Upper GI endoscopic abnormalities are described in 54–64 % of children with Crohn's disease [6, 14], the antrum being the most common site of gastric disease, with about 20 % of children with CD having isolated gastric involvement on upper endoscopy. The most commonly observed mucosal abnormalities were gastric body erythema and oedema (79.3 %) along with antral mucosal nodularity (79.3 %); less common were polyps and ulcers. Upper endoscopic changes were also noted in 50 % of patients with UC [6].

In adults other gastroduodenal lesions in CD are also reported, e.g. aphthoid, serpiginous or longitudinal ulcers (in contrast to peptic ulcers, which are round or oval).

Furthermore, conventional endoscopic studies of the gastric mucosa do not exclude FEG, as around 70 % of children with FEG are found to have endoscopically normal gastric mucosa [12].

There is still significant confusion among clinicians in the reporting of endoscopic findings. A lack of standard and validated terminology has hampered the development of clear diagnostic features, with a huge range of descriptive terms being used to describe similar changes. In addition, some authors report 'oesophagitis/gastritis/duodenitis' as endoscopic findings, when these are clearly histological descriptions. Instead, endoscopists should accurately, systematically and rigorously document what is seen at endoscopy. Descriptive terminology with clear landmarks should be used – terms such as erythema, erosion and haemorrhage have clear definitions and are widely understood concepts that are easily reproducible.

Histological Findings in Gastric IBD

Nonspecific microscopic inflammation of the upper GI tract was found in 55 % of CD patients and 60 % of UC patients in a well-conducted, prospective study [7]. These authors also found *H. pylori* infection was present in gastric IBD patients with a frequency almost equal to that of children with recurrent abdominal pain. *H. pylori* was found in 19 % of children with UC and in 12 % of those with CD. Histological lesions were frequently seen in patients with normal endoscopic appearances, as 44 % of children with CD had nonspecific inflammation and 24 % had granulomas in the presence of a normal macroscopic mucosa [7]. In UC, 58.3 % had microscopic nonspecific inflammation with endoscopically normal mucosa, whilst none had granulomas. A definitive diagnosis of CD could not be made on the basis of nonspecific inflammation found in the stomach or upper GI tract.

Specific lesions such as giant cell granulomas or mucosal ulcers in the stomach help to confirm the diagnosis of CD where there is diagnostic dilemma.

It is estimated that microscopic findings at upper endoscopy may change a diagnosis to CD in 11–29 % cases [3, 6, 14].

Severe partial villous atrophy and increased intra-epithelial lymphocytes in the duodenum were reported in up 15 % of subjects.

In a study where pathologists were blinded to the clinical diagnosis, Tobin et al. found that in 45

children with IBD and 22 controls, endoscopic gastroduodenal ulceration, partial villous atrophy and an increase in intra-epithelial lymphocytes were equally common in UC and CD. Furthermore histological oesophagitis and duodenitis were not significantly more common in CD than UC. Mild gastric inflammation was seen in nearly 92 % cases with CD, whilst only 27 % had moderate-to-severe inflammation. Only 12 % of CD patients had gastric granulomas. Interestingly 4 of 11 patients with upper GI granulomas did not have colonic granulomas, re-emphasising that upper GI investigation can be crucial to achieve an accurate diagnosis. Of children with UC, 69 % had mild gastritis. Identification of non-caseating granulomas is almost always diagnostic of CD, but differentiation from other granulomatous gastritides is important. The group concluded that severe inflammation and other abnormalities occur in the proximal GI tract in both conditions [9].

In all cases of gastric inflammation where IBD is suspected, infection with *Helicobacter pylori* should also be definitively excluded [9].

A smaller retrospective review of five paediatric cases showed gastroduodenal inflammation in UC [8]. All of them had confirmed chronic active gastritis on histology, and none of them had non-caseating granulomas. All five children had been given a presumptive diagnosis of CD based on the presence of these changes together with pancolonic inflammation. All patients failed multiple medical regimens and finally required a proctocolectomy. Analysis of the resection specimen finally confirmed a diagnosis of UC in all.

In a 7-year retrospective study of children with IBD, a significant number of patients had endoscopic and histological abnormalities in the upper GI tract. As before, the stomach was the most common site affected histologically (86 % in CD and 78 % in UC). Inflammation was more severe in CD compared to UC; granulomas were more commonly detected in the stomach than elsewhere in the GI tract. Nine out of 23 patients had granulomas solely in the upper GI tract, which was the key to establishing a diagnosis [14].

Microscopic gastric lesions termed ‘focally enhanced gastritis’ (FEG) have been described as a common finding in CD [5, 12]. However this finding has also been described in other conditions. In a retrospective case-controlled study, FEG was present in 65.1 % with CD and 20.8 % children with UC as opposed to 2.3 % children without IBD and 2.6 % children with *H. pylori* [12].

Larger FEG foci harbouring neutrophilic infiltrates are more characteristic of children with IBD. The term ‘Crohn’s gastritis’ has been used to describe this pattern of gastric inflammation; however as very similar findings were seen in patients with UC, the term ‘Crohn’s gastritis’ is now obsolete, there being no truly pathognomonic features. Interestingly treatment with steroids or five ASAs does not affect the incidence of FEG [12].

Classical granulomas may not always be present in gastric Crohn’s disease. Griffiths et al. reported that only 3 out of 10 cases of gastric CD had typical granulomas [15]. Similarly Ruuska et al. reported in their prospective study that granulomas were found in the stomach in only 8 out of 32 cases of CD who had endoscopic or histological changes in the stomach [16]. Thus the absence of non-caseating granulomas in gastric biopsies does not exclude a diagnosis of CD. Nonspecific inflammation remains very common in both conditions. Others also suggested that recognition of a granuloma and/or focal gastritis in *Helicobacter pylori*-negative biopsies should prompt further investigation towards Crohn’s disease [5].

Despite these apparent similarities, a retrospective, 2-year, blinded case series was able to correctly identify 43 out of 56 patients with CD on the basis of gastric biopsies alone. They identified discrete patterns of inflammation on the gastric biopsy that were highly suggestive of CD although none were absolutely diagnostic; they concluded that a single well-formed granuloma on a background of otherwise normal histology or focal glandulitis/glandular abscess formation is enough to suggest a diagnosis of CD. They also indicated that eosinophilic infiltrates in the lamina propria were also specifically indicative of CD (in 19 cases with no false positives identified.) They identified *H. pylori* in 18 out of 56 patients with CD [17].

A larger paediatric study reported abnormal antral histology in almost similar proportions of

children and adolescents with Crohn's colitis and ulcerative colitis (92 % versus 75 %). Focal antral gastritis was more common in patients with Crohn's colitis than ulcerative colitis (52 % versus 8 %; $p = 0.013$). Granulomas were found in antral biopsies from 15 out of 25 patients with Crohn's colitis versus none in subjects with ulcerative colitis ($p < 0.001$). The colonoscopic diagnosis of five (14 %) patients (four indeterminate, one ulcerative colitis) was changed to Crohn's disease by the finding on gastric antral biopsy of granulomatous inflammation not found in colonic biopsies. Nonspecific antral gastritis was found to be common in all forms of chronic colitis [10].

Differential Diagnosis

It is more common to find eosinophilic infiltration in CD than in UC; however eosinophils may of course represent a primary disease process in their own right. Although some diagnostic confusion remains, eosinophilic gastritis/gastroenteritis should also be considered in the differential diagnosis of gastric CD. It can be difficult to make the latter diagnosis on mucosal biopsies alone; however a clinical history of atopy, blood investigations (peripheral eosinophilia, elevated serum IgE) and histological findings showing predominant eosinophilic infiltration of the glandular epithelium (as opposed to neutrophils in CD) should help distinguish eosinophilic disease from IBD [18].

It is also important to consider and exclude any associated or isolated bacterial or fungal infections of the stomach using specific staining on the biopsy samples [17]. In this retrospective blinded case series, 10 out of 56 cases thought to have gastric CD on initial histology had an alternative diagnosis on independent histologic review. One case each had actinomycosis (with granulomas/focal neutrophilic glandulitis/glandular abscess), chronic granulomatous disease (focal glandulitis/glandular abscess), gastric abscess of unknown aetiology and pseudopancreatic cyst with concurrent active gastritis, and six cases had focal active gastritis favouring an infectious pathology. This study concluded that gastric CD should be highly considered in *H. pylori*-negative biopsies showing the above changes.

Other Investigations

Low albumin levels, anaemia and elevated inflammatory markers can be found in CD patients with gastric involvement but do not occur any more or less than in other children with CD [15]. However the presence of any of these findings with even minor histological gastric abnormalities should prompt a thorough hunt for a diagnosis of CD. Particularly Lenaerts et al. showed that only 9 % of the children and adolescents with upper GI CD had normal albumin levels compared to about 30 % without upper GI disease [4].

Barium contrast radiology is only really sensitive at detecting anatomic abnormalities (stenosis/stricture) and hence is of very limited use in investigating gastric Crohn's disease. A simple barium contrast meal is commonly normal in gastric CD [7]; however it can occasionally show irregular antral mucosa and cobblestone appearance [15]. Other possible radiological findings include thickened mucosal folds, nodularity and rarely stenosis of gastric outlet/duodenum. Cross-sectional imaging (MRI/CT) has the advantage of being able to assess gastric wall thickness as a measure of local transmural inflammation, although ultrasound in experienced hands may also have a role to play.

Given the limited response that the gastric mucosa has to insult and the obvious lack of pathognomonic endoscopic features for any one condition, endoscopists must remain open-minded and cautious in the interpretation of their macroscopic findings. The temptation to provide immediate feedback for patients and families should be resisted until discussion with an expert pathologist has occurred. The clinico-pathological meeting has become an essential part of making a diagnosis in most paediatric gastroenterology units. This exchange between endoscopist and pathologist allows frequently

subtle endoscopic findings and histological appearances to be put into an appropriate clinical context. This prevents either endoscopic features per se or histological reports alone dictating the management plan for the child.

Summary

Upper gastrointestinal involvement is common in paediatric IBD. Endoscopic abnormalities are more prevalent in Crohn's disease, whilst histological abnormalities appear equally common in both conditions. Although the presence of granulomas on upper endoscopy has clear diagnostic value, all other endoscopic and histological findings in the stomach do not distinguish between Crohn's disease and ulcerative colitis. In fact the additional detail obtained at a diagnostic upper endoscopy for IBD may well make a definitive histological diagnosis more difficult. The ease and facility of endoscopic tissue samples make it more important than ever to have an active dialogue between clinicians and pathologists. Whilst more microscopic data may increase histological uncertainty, the clinical context remains key in making appropriate and timely treatment decisions.

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Autoimmune Gastropathy

125

Ed Giles and Nicholas Croft

Introduction

Autoimmune gastropathy is a broad term encompassing an overlapping group of pathological effects in the stomach, including classical autoimmune gastritis, gastric atrophy, and gastritides associated with other diseases. There are many causes of gastropathy in children that may be considered autoimmune. Many of these are discussed in detail in other chapters of this book, such as gastritis associated with inflammatory bowel disease or gastritis associated with other systemic diseases.

Definition

There is no widely accepted unifying definition to make a diagnosis of autoimmune gastropathy or gastritis in children. Classic autoimmune gastritis (AG) is characterized by the presence of gastritis with autoantibodies directed against the parietal cell [1]. This condition, which is extremely rare in children, is a leading cause of vitamin B12 (cobalamin) deficiency in adults.

The term gastric atrophy (GA) is sometimes used interchangeably with autoimmune gastritis (AG) (see Table 125.1). GA refers to an endoscopic finding which is confirmed by histology, as described in adult pathology scoring systems and also applied to children. Histological changes are of corpus inflammation and atrophy, but these features may also be seen in other conditions and are therefore not specific [2]. GA in adults is associated with progression to metaplasia and risk of subsequent malignancy [1], but this significance is not certain in children. There is a lack of consistency in the degree of inflammation found in children with a diagnosis given of GA, reflecting lack of certainty about this condition in pediatric practice [3].

Etiology

The underlying cause of AG, like many autoimmune diseases, is unknown. The pathophysiology of parietal cell antibody (PCA)-positive AG appears to be T-cell mediated, with the H+K+-ATPase (proton pump) as the target autoantigen [4]. Parietal cells are lost from the gastric mucosa [5]. In adults, the natural history in adults appears to be slow but steady progression from atrophic gastritis to pernicious anemia over many years [6].

Pernicious anemia is a megaloblastic anemia due to vitamin B12 malabsorption caused by intrinsic factor deficiency [7]. Intrinsic factor is a glycoprotein produced by gastric parietal cells that binds dietary vitamin B12. The vitamin B12-intrinsic factor complex is absorbed in the

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Table 125.1 Comparison of autoimmune gastritis (AG) and gastric atrophy

Findings	Autoimmune gastritis	Gastric atrophy
Clinical	Pernicious anemia (in long term)	Non-specific symptoms
Endoscopic	Atrophy spares antrum	Atrophy throughout stomach
Histology	Mononuclear cell infiltrate in submucosa and LP	Atrophic submucosa
Blood	+ve autoantibody to PC +/or IF	*H. pylori* serology association
Other	Schilling test positive	Schilling test negative

LP lamina propria, *PC* parietal cell, *IF* intrinsic factor

terminal ileum after binding to intrinsic factor receptors. The progression from autoimmunity to anemia is usually over decades. Childhood pernicious anemia is not associated with chronic gastric atrophy but is usually the result of a genetically determined failure to secrete intrinsic factor or secretion of a defective intrinsic factor [5]. In a rare case of antibody-positive pernicious anemia in a child, there was no evidence of gastritis [8].

It has been suggested that *Helicobacter pylori* could be implicated in the pathogenesis of autoimmune gastritis [9, 10]. Historically, it was believed that AG was a noninfective cause of gastric atrophy affecting the fundus and body of the stomach but sparing the antrum. This is in contrast to gastric atrophy, which was thought to be caused by *H. pylori* and affecting the whole stomach [7]. There has been a suggestion that in gastric atrophy with antral sparing, the autoimmunity may be triggered by molecular mimicry (i.e., after *H. pylori* infection) [11]. The type of gastric atrophy in *H. pylori* infection is related to lifestyle factors and also the particular antigen types of the bacteria [12]. However, a study looking at the relationship between H. pylori and autoimmune gastritis in over 200 children found only three patients with positive PCA, and there was no clear association between H. pylori serology and PCA antibody positivity [13]. The relationship between H. pylori and AG thus remains unclear, particularly in children.

Incidence

As there is no clear definition, the incidence of autoimmune gastritis in children is not known. However, it is relatively more common in patients with other autoimmune diseases. Juvenile patients affected with autoimmune thyroid disease show a 14–30 % prevalence of parietal cell antibodies (PCA), and some of these patients have endoscopic and histological features of AG [14, 15]. In a study of 177 patients in the pediatric age group, 6.8 % were PCA positive, but none of the patients had AG [16].

A review of the literature regarding the prevalence of gastric atrophy in children showed a range from 0 % to 70 %, although the higher figures seem to be isolated [3]. Most of the studies included are related to *H. pylori* infection, but even in this group, the incidence appears to be from 0 % to 4 %. Interestingly, in all the studies included, the vast majority of cases were older children, and there were only a handful of individual cases of gastric atrophy in young children.

Clinical Presentation and Management

Diagnosis

Clinical manifestations of AG are not well characterized in children. In adults, they relate to the symptoms of pernicious anemia, which are insidious, and are related primarily to the megaloblastic anemia. They also include neurological features of demyelination and many nonspecific gastrointestinal symptoms and signs.

Endoscopically, there may be gastric atrophy which spares the antrum, but this is not universally found [7]. Biopsy specimens show a mononuclear cellular infiltrate in the submucosa extending into the lamina propria between the

gastric glands [5]. Histological changes rely on appropriate biopsies being taken. The updated Sydney System advises five biopsies – two from the antrum, two from the body, and one from the incisura [2]. Unless there is a high degree of suspicion macroscopically on endoscopy, it is unlikely that all these biopsies would be routinely taken in pediatric practice, which may affect the prevalence data.

Blood tests are required, as autoimmune gastritis is classically characterized by gastric atrophy, achlorhydria, low serum pepsinogen I, and high serum gastrin (due to hyperplasia of gastrin-secreting cells) [17]. Autoantibodies to parietal cells and their secretory product, intrinsic factor, are present in both the serum and in gastric juice.

Previously pernicious anemia was diagnosed by the now largely obsolete Schilling test. This was measuring urinary vitamin B12 before and after administration of vitamin B12 with intrinsic factor. Now the autoantibodies are relied upon for diagnosis, although sensitivity and specificity of various different forms of tests varies [7].

Treatment

Given the rarity of the disease in children, there is little published on specific treatments. The mainstay of treatment for adults with autoimmune gastritis is treatment of the vitamin B12 deficiency with replacement injections [7]. Early studies suggested that immunosuppression, specifically prednisolone and azathioprine can be used to halt progression of the autoimmune disease to the clinical entity of pernicious anemia [18, 19].

Natural History

The classic progression from autoantibody production to gastritis and then to the development of pernicious anemia is over decades in adults. The risk of developing gastric cancer from gastric atrophy has been quoted at 0.1% per year, and surveillance is warranted [20]. Gastric carcinoma is exceedingly rare in pediatrics but has been reported in association with pernicious anemia [21]. Untreated pernicious anemia may lead to the neurological consequences of vitamin B12 deficiency, such as reversible ataxia [8].

Other "Autoimmune Gastropathies"

Celiac Disease

Celiac disease is diagnosed by classic histological changes in the distal duodenum and jejunum. The majority of pediatric patients are found to have gastritis, which is either lymphocytic (increased number of intraepithelial T-lymphocytes), or chronic gastritis, or both [22, 23] (Fig. 125.1). These histological features seem to resolve as the celiac disease is treated [22]. However, the findings have not been related to any particular clinical features or presentation of the disease. There is clearly overlap with the diagnosis of lymphocytic gastritis [24], which is described below.

Allergic Gastritis

In contrast to pure eosinophilic gastritis, this condition is part of the spectrum of allergic gastrointestinal disorders. Cow's milk protein is the allergen most commonly associated, although there is substantial crossover with soya bean allergy, as well as other allergens [25]. Symptoms include vomiting, irritability, and poor weight gain [26].

To confirm a diagnosis of food allergic gastritis would require a formal food challenge with associated endoscopic findings, although in practice the diagnosis is often suspected on history and treated with elimination of allergens in the diet [25]. If endoscopy is performed, histological findings are of eosinophilic infiltrate in the lamina propria, as well as increased numbers of lymphocytes, plasma cells, and neutrophils [2, 27]. The treatment is through elimination of the appropriate antigen in the diet, including sometimes in the diet of a breastfeeding mother. This can involve the use of a hypoallergenic infant formula [26]. The natural history of this condition is to resolve with age [28].

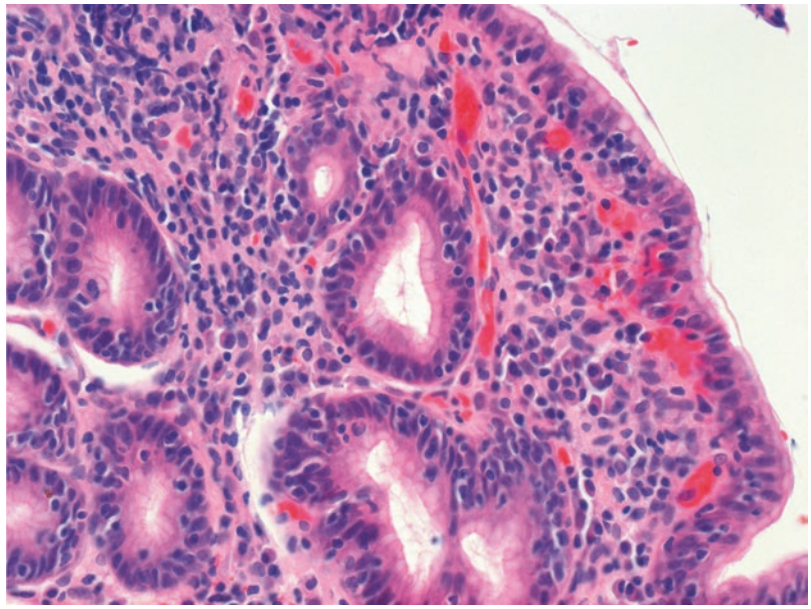

Fig. 125.1 High-power photomicrograph showing lymphocytic gastritis in association with celiac disease. There are clusters of lymphocytes in surface and gland epithelium, together with a chronic inflammatory cell infiltrate in the lamina propria (Image kindly provided by Professor Paola Domizio)

Eosinophilic Gastritis

This is a rare disorder even in adults and is usually grouped together with eosinophilic gastroenteritis [29], although it is likely they are distinct clinical entities. Eosinophils are seen in normal gastric biopsies making diagnosis even more difficult. The condition can either be primary or secondary to a systemic disease or infection, including to *H. pylori*. Primary or idiopathic eosinophilic gastritis is suggested to have an allergic etiology, and treatment is often directed at potential allergens or medications that alter the allergic response [30].

Ménérier's Disease

This is also a rare disorder characterized by a protein-losing hypertrophic gastritis. In children, the average age of presentation is 5 years. The clinical picture is an abrupt onset of edema, vomiting, abdominal pain, and anorexia [31]. Gastroscopy shows giant hypertrophy of the mucosal folds in the stomach [29]. Microscopic findings may include hypertrophic dilated gastric glands filled with mucous and an inflammatory infiltrate with the gastric mucosa [31]. Compared with adult Ménétrier's disease, in childhood the disease is usually self-limiting. CMV has been implicated as the cause in a third of pediatric cases [32].

Varioliform Gastritis

Exceptionally rare in children, this condition is most striking in innumerable prominent nodules on the fundus and proximal body of the stomach, which may have a central crater or erosion [27]. There is some evidence that there may be an allergic basis for this condition, with high total IgE levels and eosinophilia [33]. There is also overlap with lymphocytic gastritis as described below [34].

Lymphocytic Gastritis

This condition is defined by the recognition of >25 intraepithelial lymphocytes per 100 surface epithelial cells [29]. This is a histological

diagnosis with a lot of overlap with other conditions [22]. For example, approximately 50% of children with untreated celiac disease have lymphocytic gastritis [24], and it is also seen in varioliform gastritis [34].

Henoch-Schönlein Gastritis

Henoch-Schönlein purpura (HSP) is the most common systemic vasculitis in children. It is a vasculitis mediated by IgA deposition. It is diagnosed by criteria which include palpable purpura plus one of abdominal pain, arthralgia or arthritis, renal involvement, or IgA deposition [35]. These IgA deposits can develop anywhere in the gastrointestinal tract, but the small bowel is the most common [36]. If endoscopy is performed, gastritis may be found, but the features are usually nonspecific [25]. However, purpuric-type lesions may be seen in the stomach and histologically show a leukocytoclastic vasculitis, with immunostaining revealing IgA deposits [37]. These features are similar to what is seen in the skin lesions. HSP is usually self-limiting, and no medical treatment (including corticosteroids) has been shown to consistently affect the gastrointestinal manifestations [35].

Graft-Versus-Host Disease

Graft-versus-host disease (GVHD) can be acute or chronic, with acute occurring in the first 100 days following transplantation, during or soon after engraftment. It generally refers to damage to the skin, gastrointestinal tract, or liver which is graft T-cell-mediated targeting host antigens [38]. Acute GVHD of the GI tract usually presents with diarrhea which is secretory in nature and often of great volume [38]. Other clinical features include anorexia, nausea and vomiting, abdominal pain, and bleeding due to mucosal ulceration (and carry a worse prognosis) [39]. Given the multiple possible causes of gastrointestinal symptoms in this group of patients, endoscopy and biopsy are required to establish the diagnosis [40]. The classic histological feature is epithelial apoptosis [41]. This must be differentiated from the similar features of viral infections, particularly CMV, which can also cause pathology in this group of patients. Chronic GVHD has much more varied presentations, but typically affects the esophagus in the GI tract, and may present with strictures [25, 38]. There are no specific histological features of chronic GVHD [41].

Inflammatory Bowel Disease

Gastritis is a feature seen in both Crohn's disease and ulcerative colitis, but this will be discussed in great detail in. Crohn's disease is the most common cause of granulomatous gastritis.

Other Granulomatous Gastritides

Granulomata in the stomach are a rare finding and are usually a feature of Crohn's disease [42]. However, in an endemic area, *H. pylori* has been implicated as a leading cause, especially when found associated with ulceration [43]. Eradication of the *H. pylori* leads to resolution of the granulomata, but it is not clear why a small number of patients develop this feature [44].

Other causes included sarcoidosis, chronic granulomatous disease, tuberculosis, syphilis, histoplasmosis, parasitic infections, vasculitis-associated granulomata, tumors (including adenocarcinoma and lymphoma), lymphocytic gastritis, and foreign-body associated granulomata [27, 42]. Sometimes a diagnosis of idiopathic granulomatous gastritis is made, but it is uncertain whether this is a true clinical entity.

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Systemic Disease Affecting the Stomach

126

Sue Protheroe

Introduction

The stomach is a complex organ that performs three basic physiological processes to contribute toward digestion, i.e., secretory activity, endocrine function, and motility. The stomach may respond to systemic disease with the development of macroscopic and microscopic mucosal changes such as gastritis or gastropathy secondary to vasculitis or infiltrative disease. Gastritis is defined as microscopic evidence of inflammation affecting the gastric mucosa and can be primary or secondary, based on the underlying etiology. Primary gastritis may be due to infection with the organism *Helicobacter pylori*. Secondary gastritis and ulceration may be clinically and often histologically distinct and gastric biopsy offers a relatively accessible source of information to support a clinical diagnosis. Gastric distension and emptying involve a number of complex interactions between myenteric, neurologic, and hormonal factors. Although symptoms related to gastric dysfunction such as nausea and vomiting are common in children, primary motility disorders of the foregut are relatively rare. Delayed transit disorders may be secondary to conditions that involve only the stomach (gastroparesis) or be part of a more generalized gastrointestinal motility disorder and reflect a disease process affecting one of more of the neurogenic, smooth muscle, or hormonal factors that regulate gastric emptying. The objective of this chapter is to review various systemic conditions affecting the stomach, highlighting where gastric biopsy can be useful to diagnose or evaluate a systemic disorder. Although there is no single satisfactory description of all systemic disease involving the stomach, an etiology-based classification (Table 126.1) provides a practical approach for directing both further investigations and unifies the findings of the endoscopist and the histopathologist when mucosal biopsy material is available. The overlapping nature of endoscopic or histological findings makes classification of some gastropathies into more than one category.

Systemic Vasculitis

Systemic vasculitides are a group of disorders with multiorgan involvement that can involve local or diffuse pathologic changes in the gastrointestinal tract [1]. The extent and clinical course of disease depend on the size and location of the affected vessel and the histological characteristics of the lesion (Table 126.2). Gastrointestinal clinical manifestations are diverse: nonspecific paralytic ileus, mesenteric ischemia, submucosal edema and hemorrhage, and bowel perforation or stricture.

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Table 126.1 Systemic disease and the stomach

Pathophysiology of systemic disease affecting the stomach	Condition
Vasculitis	Henoch-Schonlein purpura, Kawasaki's disease, Beçhet's disease, rheumatoid arthritis, SLE, PAN
Granulomatous	Crohn's disease, vasculitis-associated inflammation, Wegener's granulomatosis, Churg-Strauss syndrome
Infectious and postinfectious disease	Infectious (tuberculosis, parasitic, histoplasmosis, syphilis, Whipple's disease, viruses (e.g., CMV, EBV, VZV)
Immune deficiency/dysregulation	Common variable immune deficiency, severe combined immune deficiency, X-linked agammaglobulinemia, chronic granulomatous disease
	Sarcoid
	Langerhans cell histiocytosis (LCH)
	Graft versus host disease
	Posttransplant lymphoproliferative disease
Autoimmune and autoinflammatory disease	Celiac disease
	Autoimmune enteropathy including IPEX
	Autoimmune hepatitis type 1 diabetes mellitus
	Autoimmune thyroiditis
	Autoimmune polyendocrine syndrome types 2 and 3
	Familial Mediterranean fever
Endocrine	Hypothyroidism, type 1 diabetes
Renal	Renal failure
	Cystinosis
Allergic	Cow's milk protein intolerance
Vascular	Hereditary hemorrhagic telangiectasia, portal hypertension
Stress related	Respiratory failure, hepatic failure, cardiac failure, multiorgan failure, sepsis, trauma, burns
Neoplasia	Gastrointestinal stroma tumor (GIST) in Carney's triad (gastric epithelioid stromal sarcoma, extra-adrenal paraganglioma, and pulmonary chondroma)
	Gastric lymphoma in primary immunodeficiency
	Non-Hodgkin's lymphoma/GIST (leiomyosarcoma) in HIV
Polyps	Juvenile polyposis syndrome
	Familial adenomatous polyposis
	Peutz-Jeghers syndrome
	Gardner's syndrome

Table 126.2 Vasculitis and the gastrointestinal tract

Size of vessel	Vasculitis
Large vessel	Giant cell arteritis
	Takayasu arteritis
Medium vessel	Kawasaki disease, PAN
Small vessel	Henoch-Schonlein purpura, Beçhet's, disease, SLE, RA, Wegener's granulomatosis
	Churg-Strauss syndrome

The most common vasculitides in children are self-limiting conditions: Henoch-Schönlein purpura and Kawasaki disease. Lifelong and chronic vasculitides (e.g., giant cell arteritis, Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome, polyarteritis nodosa, and Takayasu arteritis) are rarely seen in children [2]. Nevertheless, the possibility of vasculitis should be considered whenever possible mesenteric ischemic changes occur in young patients at unusual sites (e.g., the stomach, duodenum, and rectum) and have a tendency to concomitantly involve the skin or genitourinary system. Clinical manifestations usually provide the diagnosis, but endoscopic findings in the stomach may help

establish the specific cause since radiologic findings in various types of vasculitis often overlap considerably and have limited value in making a specific diagnosis [3].

Henoch-Schlonlein Purpura

Henoch-Schlonlein purpura (HSP) is the most common childhood vasculitis comprising up to 90 % of all cases. Peak incidence is 4–6 years and 90 % occur before the age of 10. HSP is characterized by nonthrombocytopenic palpable purpura, arthritis or arthalgia, and gastrointestinal and renal involvement. Antigen-antibody (IgA) complexes activate the alternate complement pathway, resulting in inflammation and small vessel vasculitis without a granulomatous reaction [4]. The etiology is unclear but it is associated with infections (group A beta hemolytic streptococci, *Staphylococcus aureus*, *Mycoplasma*, human parvovirus B19), medications (clarithromycin, paracetamol), and vaccinations (pneumococcal, influenza). Cutaneous involvement is the most common presentation and is seen in 50 % of cases as the presenting sign and usually precedes gastrointestinal manifestation, although in one forth of cases, skin lesion occurs after gastrointestinal manifestations. Diffuse, abdominal pain colicky is the most common symptom, and nausea, vomiting hematemesis, melena, and hemochezia are secondary to mesenteric vasculitis which causes extravasation of blood into the interstitial spaces resulting in edema and hemorrhage. Rarely ileocecal intussusception, ischemic necrosis of the bowel, or massive gastrointestinal bleeding can occur. Positive fecal occult blood and raised stool α1-antitrypsin suggest mucosal injury even in the patients without gastrointestinal symptoms [4]. HSP is a clinical diagnosis, but when the presentation is atypical, if skin lesions are absent, or when gastrointestinal symptoms are severe or persistent, gastrointestinal mucosal biopsy may be helpful useful in early diagnosis [5]. The duodenum is most commonly involved, but changes noted in the gastric antrum include erythema, edema, petechiae, superficial, multiple ulcers, hemorrhage, hematoma-like protrusions, and ecchymotic lesions [6]. Histopathology shows preserved villous architecture and leukocytoclastic vasculitis with IgA deposition on immunofluorescence with neutrophilic and eosinophilic infiltrates. Crohn's disease and Wegener's granulomatosis can also present as leukocytoclastic vasculitis. High-resolution ultrasound can identify bowel wall abnormalities such as submucosal thickening and loss of differentiation [7]. Treatment of HSP reflects its self-limiting nature in 94 % of children and specific therapy is not usually required. Oral steroids are indicated in patients with severe colicky abdominal pain, renal, scrotal, and testicular involvement or severe rash. Early steroid therapy has been shown to decrease gastrointestinal symptoms within 2 days compared to 12.3 days in patients without steroids and may decrease recurrence of gastrointestinal bleeding or intussusception [8]. Although corticosteroids alleviate the symptoms, they seem not to alter the clinical course of extra renal symptoms during 6 months of follow-up [9].

Kawasaki's Disease

Kawasaki disease (KD) is a vasculitis of unknown etiology. The diagnosis is based upon the most frequent symptoms of fever and abnormalities in the oral mucosa, and the most important complication is the characteristic damage to coronary arteries. The essential lesion in Kawasaki's disease is an arteritis initially involving small arteries and later the medium and large vessels which can target the gastrointestinal tract. Complications secondary to necrosis of the intestines can affect the stomach, duodenum, jejunum, liver, and gall bladder causing acute hydrops [10, 11].

Juvenile Chronic Arthritis

Children with juvenile chronic arthritis (JCA) frequently presents with epigastric pain and dyspepsia which have largely been attributed to the use of nonsteroidal anti-inflammatory

drugs (NSAIDs), the mainstay of treatment in JCA. Macroscopic endoscopic lesions such as ulcers and infection by *Helicobacter pylori* have been frequently observed in this population who may be asymptomatic [12]. It is suggested that endoscopic evaluation of children with JCA receiving NSAIDs should be considered at least in symptomatic cases [13, 14]. Long-standing juvenile rheumatoid arthritis can be associated with amyloidosis, although the condition is rare in these under 15 years of age. Amyloid is deposited in the gastrointestinal tract and can be detected by rectal or gastric biopsy. Serial gastroduodenal mucosal biopsy specimens have been used to demonstrate removal and sustained decrease in amyloid deposits after therapy with agents such as anti-TNFα [15].

Systemic Lupus Erythematosus

Gastrointestinal vasculitis may contribute to morbidity and mortality in systemic lupus erythematosus (SLE) [16]. Dysphagia and heartburn are the most common manifestations. Since virtually all children with SLE require treatment with NSAIDs and/or corticosteroids, it is difficult to differentiate treatment-caused gastrointestinal manifestations and gastritis due to the disease itself [17]. However, immune complex deposition in the arteriolar walls has been observed in the inflammatory infiltrate in the stomach and duodenum from children during disease exacerbation [18]. Children with SLE on long-term NSAIDS may need to be maintained on long-term gastroprotective agents such as a proton pump inhibitors and use of specific COX-2 inhibitors which have fewer gastric side effects than conventional NSAIDs. Ischemic bowel ulcers, attributable to vascular lesions of SLE in children, can be complicated by perforation and secondary invasion by opportunistic organisms [17]. Invasive gastric mucormycosis, a rare but usually fatal fungal infection in SLE, occurred in a child with systemic lupus erythematosus who was successfully treated with aggressive antifungal therapy [17]

Polyarteritis Nodosa

Polyarteritis nodosa (PAN) rarely presents in childhood. Upper gastrointestinal bleeding can occur due to ulcers in the stomach (Dieulafoy's lesions) [18, 19]. Multiple visceral aneurysms causing colitis and jejunitis have been reported in a child with PAN. The diagnosis was established with multidetector CT and CT angiography [20]

Beçhet's Disease

Beçhet's disease (BD) is a chronic multisystem vasculitis that can involve both the arteries and veins of almost any organ and is characterized by mucocutaneous, articular, neurological, gastrointestinal, and ophthalmological lesions. Pediatric Beçhet's is rare and is diagnosed in the presence of recurrent oral aphthosis plus one of the following: genital ulceration, erythema nodosum, folliculitis, pustulous/acneiform lesions, positive pathergy test, uveitis, venous/arterial thrombosis, and family history of BD [21]. Intestinal Beçhet's disease is less common and is characterized by discrete, deep punched-out ulcers, most commonly located in the ileocecal region, with a tendency to bleeding and perforation. In comparison with Crohn's disease, less inflammation is seen in the area surrounding an ulcer and granulomas are not seen [22]. Gastric involvement is thought to be rare, although in asymptomatic patients screened with routine endoscopy, abnormalities in the upper GI tract were noted including gastritis, gastric ulceration [23], and perforation [24]. Abnormalities might not be specific for the disorder since medications such as steroids or aspirin might aggravate ulcer formation.

Granulomatous Gastritis

Granulomatous gastritis is a notable feature in gastric biopsies. Histological identification requires consideration of potential causes (Table 126.3) and distinction from the common histological appearance of gastritis and gastric mucosal ulceration of Crohn's disease. Chronic

Table 126.3 Systemic diseases associated with granulomatous gastritis

Systemic diseases associated with granulomatous gastritis	
Inflammatory bowel disease	Crohn's disease
Infectious	*Helicobacter pylori*, mycobacterium tuberculosis, parasitic, histoplasmosis, syphilis, Whipple's disease
Vasculitis-associated inflammation	Wegener's granulomatosis, Churg-Strauss syndrome
Infiltrative/immunological	Sarcoid
	Langerhans cell histiocytosis
	Chronic granulomatous disease

active gastritis is not uncommonly found in ulcerative colitis [25].

Vasculitis-Associated Inflammation with Granulomata

Wegener's Granulomatosis

Wegener's granulomatosis (WG) is a systemic vasculitis, involving the respiratory tract and the kidneys [26]. The incidence of childhood WG during is comparable to reports in adults (6.39 cases/million/year) and it seems to be increasing. Typical histopathological features are a polymorphous vasculitis often associated with necrosis and granulomatous inflammation. Histological proof of necrotizing vasculitis is dependent on the depth of the biopsy and can be missed since the vessels that are usually affected in WG are present in the submucosa and may not be accessible on biopsy. Crohn's disease may be suspected due the histological findings of granulomatous gastritis in the presence of gastrointestinal and extra gastrointestinal symptoms, such as arthralgia, arthritis, and inflammatory changes in the eye and skin. Differentiation from Crohn's disease is supported by a positive test for antineutrophil cytoplasmic antibodies (ANCAs) with a cytoplasmic pattern (c-ANCA) and antigenic specificity for proteinase 3 (PR-3) [27]

Churg-Strauss Syndrome

Churg-Strauss syndrome is an allergic granulomatous vasculitis accompanied by asthma and eosinophilia. The lungs, skin, and nervous system are the most common sites of involvement. It is generally considered a disease of adults; occurrence in children has been reported infrequently [28, 29]. Widespread involvement of the gastrointestinal tract including gastric ulceration has been reported in adults [30].

Non-vasculitis-associated Inflammation with Granulomata

Sarcoid

Sarcoidosis is a systemic granulomatous immunological disorder of unknown etiology, with accumulation of activated lymphocytes and macrophages in any organ. The intrathoracic lymph nodes and the lung remain the most common sites of disease (90%). While gastrointestinal involvement is rare, gastric involvement is the most common [30] and can be a feature of systemic disease or in isolation. Generally the disease is asymptomatic, but pain in the epigastrium, nausea, vomiting, or hematemesis may be present. Endoscopic findings are variable: localized or diffuse hyperemia, single or multiple ulcers, with noncaseating granulomas [31]. Differentiation is required from the histological and endoscopical gastric pathologies resembling sarcoidosis (histoplasmosis, Crohn's disease). Steroids are the most appropriate treatment.

Langerhans Cell Histiocytosis

Langerhans cell histiocytosis (LCH) is a rare disease caused by a clonal proliferation of specialized dendritic-like CD1a-positive (Langerhans) cells with an unknown cause. The

large mononuclear cells accumulate forming granulomata in various organs, mainly the lung, bone, or skin. LCH of the alimentary tract is rare, but gastric mucosal biopsies in an adolescent with multiorgan LCH and striking gastric polyposis have been reported [32]. Microscopically, the gastric mucosa was expanded by discrete granulomatous microaggregates of Langerhans cells, resulting in a close resemblance to other, more common nonnecrotizing granulomatous gastritides. Abdominal tuberculosis (TB) is infrequent in the Western world and occurs more frequently among at-risk populations, elderly patients and patients with HIV infection. Abdominal TB usually manifests itself as intestinal TB, peritoneal TB, and mediastinal lymphadenitis. Gastric TB is a rare manifestation; symptoms include nausea and vomiting, iron deficiency, and weight loss. Diagnosis is made by endoscopic biopsy of the affected area in the antral region, with granulomatous chronic gastritis suggesting tubercular origin [33] (Fig. 126.1). Chronic granulomatous disease (CGD) is an additional important cause of granulomatous gastritis (Sect. 126.6).

Infectious Disease

In addition to tuberculosis, Whipple's disease is a multisystem granulomatous infectious disease. It is caused by *Tropheryma whipplei* and is transmitted by the fecal-oral route, generally in children 2–4 years of age with other enteric pathogens. The bacteria rod-shaped gram-positive actinomycete accumulates within macrophages, preferentially in the intestinal mucosa causing diarrhea, abdominal pain, and malabsorption [34]. Disease manifestation seems to be linked to immunological abnormalities of macro-

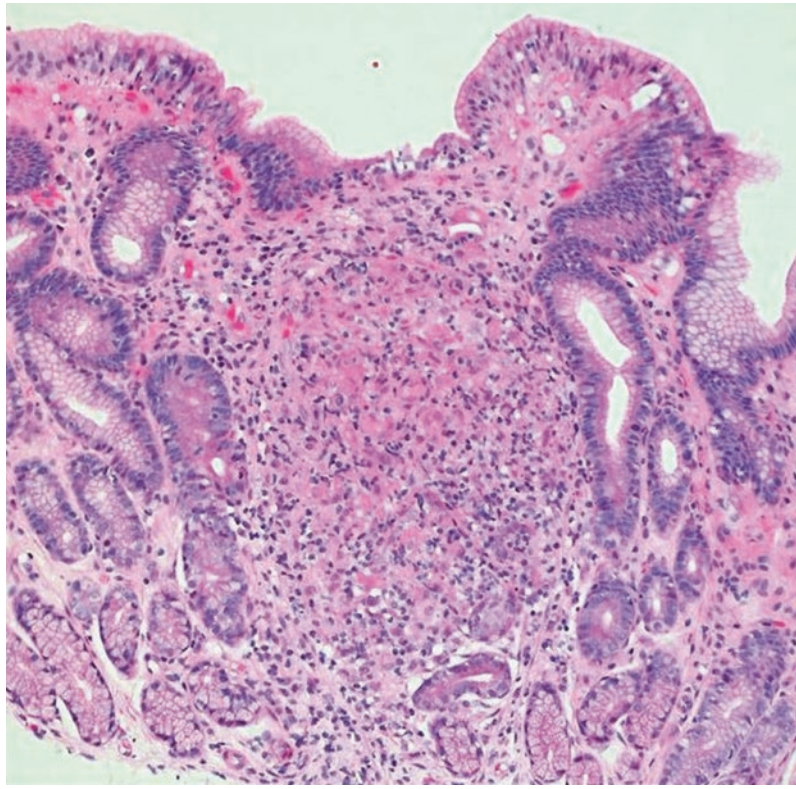

Fig. 126.1 *Mycobacterium tuberculosis*. Gastric biopsy of a child undergoing endoscopy for suspected celiac disease revealing granuloma. *Mycobacterium tuberculosis* infection and celiac disease diagnosed (H&E ×40)

phages. Gastric antral Whipple's may be found on biopsy as a granulomatous infection in the stomach with foamy macrophages with intracellular PAS-positive granules [35]. See following Sect. 126.6 for opportunistic and viral infections involving the stomach.

Immune Dysregulation

Chronic Granulomatous Disease

Chronic granulomatous disease (CGD) is an uncommon primary immune deficiency with X-linked and autosomal recessive forms. CGD is caused by a defect in phagocyte production of oxygen metabolites resulting in recurrent infections with a narrow spectrum of bacteria and fungi as well as a common set of inflammatory complications most notably including inflammatory bowel disease in the majority of cases [36]. Patients often present with enterocolitis, while ulceration and infection associated with granuloma formation (abscesses) can occur anywhere from the mouth to the anus. CGD is known to present with gastric outlet narrowing or obstruction due to inflammatory thickening in the gastric antral wall which needs to be distinguished from other causes of pyloric narrowing such as peptic ulcer disease, Crohn's disease, and gastric tumor [37]. MRI has been used to monitor gastric wall inflammation [38]. CGD has been an important disease for the development of bone marrow transplantation and gene therapy [36].

Other disorders of neutrophilic function, e.g., leukocyte adhesion molecule deficiency I where hepatic and perirectal abscesses are characteristic, should be distinguished from CGD.

Other Immune Deficiencies (ID)

Immunoglobulin A (IgA) deficiency is the most common primary immunodeficiency, with decreased serum level IgA in the presence of normal levels of other immunoglobulin isotypes. Most individuals with IgA deficiency are asymptomatic and identified coincidentally but appears to be a risk factor for infections, allergic diseases, and autoimmune conditions [39]. IgA-deficient individuals have a tendency to develop infections such as giardiasis and disorders of the gastrointestinal tract, notably malabsorption, lactose intolerance, celiac disease, ulcerative colitis, and nodular lymphoid hyperplasia [40]. Common variable immune deficiency (CVID) is the second most prevalent primary ID but clinically the most important. Increased susceptibility to infections and diminished responses to protein and polysaccharide vaccines are apparent after 24 months of age and usually in young adulthood. CVID is a combination of humoral and cell-mediated deficiency, which explains not only why so many systems are affected but also why standard therapy in the form of intravenous immunoglobulin is not always effective [41, 42].

Gastointestinal tract CVID displays a wide spectrum of histologic patterns and can mimic celiac disease, lymphocytic gastritis, acute graft-versus-host disease, and inflammatory bowel disease. The diagnosis of CVID may be suspected on the basis of the lack of plasma cells in a gastric biopsy, present in about two-thirds of patients, lymphoid aggregates poorly formed granulomas, and an increase in apoptosis [43]. Intraepithelial neutrophils were found in a subset, accompanied by various infections [cytomegalovirus (CMV), *Helicobacter pylori*, and *Cryptosporidium*]. Children with X-linked agammaglobulinemia (XLAG) have high incidence of chronic gastrointestinal complaints, most commonly diarrhea. Patients with XLAG, like CVID, manifest a spectrum of abnormalities that resemble graft-versus-host disease with apoptotic bodies and lymphocytes in crypts in gastric biopsies [44]. The primary immunodeficiences (severe combined immunodeficiency (SCID), XLAG, CVID, Wiskott-Aldrich syndrome, and ataxia telangiectasia) are associated with an increased risk of high-grade gastric lymphomas. Symptoms may be nonspecific such as abdominal pain, gastric outlet obstruction, or bleeding. Tumors require resection followed by chemotherapy/radiotherapy.

HIV and Opportunistic Infections of the Stomach

Highly active antiretroviral therapy (HAART) has dramatically decreased opportunistic infections (OIs) in HIV-infected patients. However, gastrointestinal disease continues to account for a high proportion of presenting symptoms in patients with HIV infection. An abnormal endoscopic finding confirmed by histologic, microbiologic, or a combination of these studies was reported in 72 % of children. Thirty-five percent of children had an opportunistic pathogen identified endoscopically; 65 % of these pathogens were previously undiagnosed [45]. HIV-associated non-Hodgkin's lymphoma is mainly diagnosed with advanced disease. Intestinal infection with *Cryptosporidium* sp. and *Strongyloides stercoralis* can be identified in H&E tissue stained sections of nomal-looking gastric mucosa or abnormal mucosa with gastric hyperemia, edema, and erosions.

Viral Gastritis

Cytomegalovirus (CMV) infection of the stomach is described in immune-compromised and immunocompetent individuals and is the most common opportunistic infection of the stomach. It is commonly associated with nonspecific symptoms such as epigastric pain, nausea, and vomiting. Ulcerations, erosions, and mucosal hemorrhage may be seen endoscopically, although mucosa may appear normal. Cytomegalic cells in tissue biopsies are considered the gold standard for establishing a diagnosis of CMV disease. The availability of newer, rapid diagnostic techniques such as polymerase chain reaction (PCR) detection of CMV-DNA in the stools may facilitate diagnosis, as serology studies may be misleading. Usually, only supportive care is required, but treatment with ganciclovir may be considered for severe or prolonged cases. CMV is one of the agents associated with Menetrier's disease [46]. Menetrier's disease is an uncommon disease in childhood, characterized by gastric hypertrophy and hypoalbuminemia. The most common presenting symptoms are vomiting and edema in children with protein-losing gastropathy associated with cytomegalovirus (CMV) infection [46].

Posttransplant Lymphoproliferative Disease and Opportunistic Infections

While gastrointestinal lymphoma in congenital immunodeficiency disorders is rare, posttransplant lymphoproliferative disease (PTLD) of the gastrointestinal tract is not uncommon and is associated with high mortality in transplant recipients. PTLD can occur after every kind of organ transplantation, is associated with immune suppression and EBV infection, and is predominantly in the form of a B-cell lymphoma. Pediatric patients are often EBV-seronegative pretransplant which places them at high risk [47]. EBV infection and early PTLD can be subclinical or have nonspecific signs such as fever and malaise and can affect the lymph nodes, intestine, tonsils, adenoids, or eye. Gastrointestinal PTLD occurs mostly in the stomach and duodenum and may be multifocal. Pediatric patients with PTLD with abdominal involvement have increased mortality, and rates of life-threatening complications such as bleeding, perforation, or obstruction are high [48]. Endoscopy demonstrates diffuse or nodular polypoid lesions covered with erosive mucosa (Fig. 126.2).

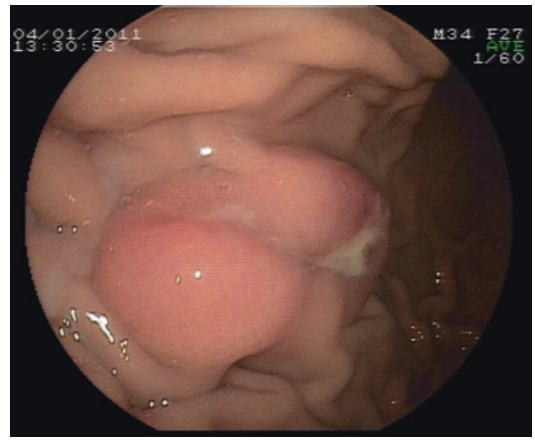

Fig. 126.2 Posttransplant lymphoproliferative disease. Gastric polypoid tumor detected in a child with upper gastrointestinal hemorrhage and fever post renal transplantation

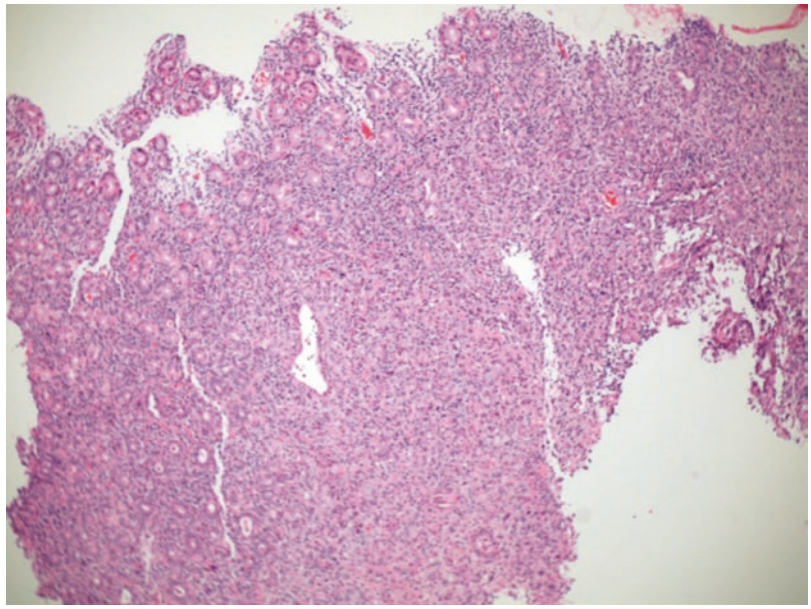

Fig. 126.3 Gastric posttransplant lymphoproliferative disease. Dense polymorphic B-cell lymphoid infiltrate expands the lamina propria (H&E ×4)

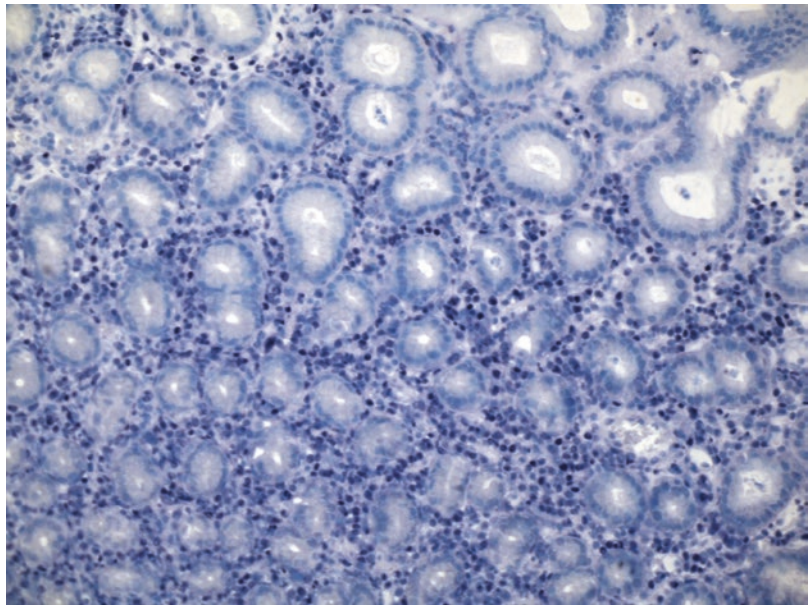

Fig. 126.4 Gastric posttransplant lymphoproliferative disease. Polymorphic B-cell posttransplant lymphoproliferative disorder – the majority of the lymphoid cells are EBER positive (EBER in situ hybridization ×20)

Mucosal biopsies reveal high-grade B-cell histology (monomorphic or polymorphic B-cell lymphoma, Burkitt lymphoma, or reactive plasmacytic hyperplasia if early [49] (Fig. 126.3). Epstein-Barr virus (EBV) in situ is demonstrated in mucosal biopsies (Fig. 126.4). Treatments include tapering of immunosuppression, viral monitoring, and antiviral interventions, surgery,

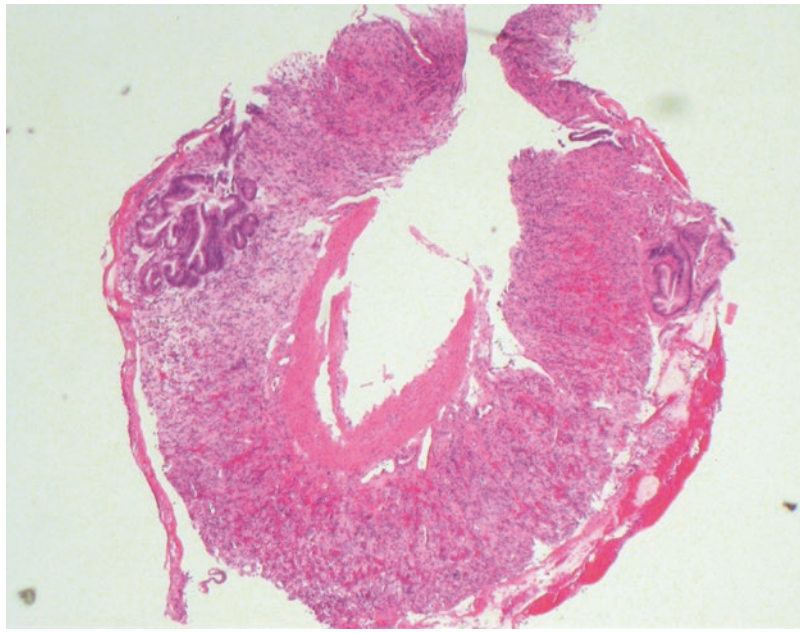

Fig. 126.5 Severe graft-versus-host disease. Complete surface epithelial denudation and subtotal loss of glands in gastric antral mucosa seen in a 14-year-old girl post bone marrow transplantation (H&E ×4)

autologous T-cell therapy, and anti-CD20 antibody (rituximab). Routine detection of increased EBV by quantitative polymerase chain reaction is used to determine the EBV viral load in the peripheral blood and is a marker for increased risk of PTLD.

In addition to CMV and EBV infections, varicella zoster-induced gastritis has been reported in the immunosuppressed posttransplant patient in the absence of herpetic skin lesions [50]. Herpetic lesions were demonstrated in the gastric antrum by endoscopy and emphasize the importance of viral-induced gastritis in the absence of skin lesions in differential diagnosis of abdominal pain in this group.

Graft-Versus-Host Disease

Accurate diagnosis of gastrointestinal graft-versus-host disease (GVHD) is important, as it contributes significantly to post-allogeneic stem cell transplant (SCT) morbidity and mortality [51]. Acute graft-versus-host disease is characterized by damage to the skin, liver, and gastrointestinal tract. Upper gastrointestinal tract disease presents with anorexia, vomiting, and dyspepsia and must be distinguished from drug or radiation toxicity. Endoscopic appearances may appear normal or show evidence of mucosal erosion, edema, and erythema and sloughing. Biopsy is required even if the mucosa appears normal, targeting the gastric fundus rather than antrum [50]. The diagnosis is made by finding mixed inflammatory infiltrate often with epithelial cell apoptosis (Fig. 126.5). Differentiation is required from the similar histological changes in viral infections such as CMV and toxicity of the pre-transplant conditioning regime. Capsule endoscopy (CE) is a novel and noninvasive means of investigating the small bowel in suspected GVHD, with a diagnostic yield of 88 % [49].

Autoinflammatory Diseases

Autoinflammatory diseases (or hereditary periodic fever syndromes) are a group of genetic disorders characterized by recurrent or persistent systemic inflammatory symptoms with

an underlying single causative gene defect [50]. They are classified as primary immunodeficiencies and must be distinguished from infectious diseases, autoimmune diseases, and other primary immunodeficiencies. Familial Mediterranean fever (FMF) is due to mutations in the Mediterranean fever (MEFV) gene and is best understood and characterized by recurring and self-limiting fever with a combination of severe abdominal pain due to peritonitis, serositis, pleurisy, arthritis, and a characteristic ankle rash. The flares typically last for up to 3 days at a time, and most patients are completely asymptomatic between attacks [51]. Gastric amyloidosis secondary to FMF in childhood has been demonstrated by deposits in endoscopic gastric biopsies, performed in view of abdominal pain [51].

Autoimmune Disease (Table 126.4)

Atrophic body gastritis or autoimmune gastritis (AG) is rare in children, but is seen in the context of other autoimmune conditions such as diabetes mellitis, autoimmune thyroiditis, and autoimmune polyendocine syndrome (APS) type 3 (a syndrome characterized by the combination of at least two autoimmune endocrinopathies) [52]. Parietal cell antibodies (PCA) are markers of AG which can be found in up to 30 % children with autoimmune thyroid disease who are positive for thyroid peroxidase antibodies (TPOAb) and in 25 % of children with type 1 diabetes mellitus (T1DM), but overt clinical AG disease is rare in children with T1DM [53]. AG results from immune-mediated destruction of specialized oxyntic glands, is restricted to the body and fundus, and shows lymphocytic infiltration of the gastric submucosa, with loss of parietal and chief cells and characteristic neuroendocrine hyperplasia [54]. The main immunological marker of AG is the presence of autoantibodies against the parietal cell (anti-parietal cell antibodies (PCA)) [55]. AG can lead to hypergastrinemia; gastrin levels reflect the degree of gastric atropy. PCA+ subjects are at increased risk for iron-deficiency anemia and atrophic gastritis, vitamin B 12 deficiency, and megaloblastic anemia. An 11-year-old boy has been reported with malabsorption and macrocytic anemia in the presence of autoimmune polyglandular syndrome (APS) type 2, which is characterized by Addison's disease, in association with autoimmune thyroid disease and/or type 1 diabetes mellitus [55].

Table 126.4 Autoimmune conditions associated with autoimmune gastritis

Organ specific autoimmune conditions associated with autoimmune gastritis	
Autoimmune gut/liver disorders	Celiac disease
	Autoimmune enteropathy including IPEX syndrome
	Autoimmune hepatitis
Autoimmune endocrine disorders	Type 1 diabetes mellitus
	Autoimmune thyroiditis
	Autoimmune polyendocrine syndrome types 2, 3

Concurrent autoimmune diseases are also common in patients with autoimmune hepatitis (AIH), an inflammatory liver disease that mainly affects females and is particularly aggressive in children. It is characterized histologically by interface hepatitis, biochemically by increased aspartate and alanine aminotransferase levels, and serologically by the presence of autoantibodies and increased levels of immunoglobulin G. It progresses rapidly unless immunosuppressive treatment is started promptly, when 80 % of patients achieve remission and long-term survival [56, 57].

Celiac disease is an autoimmune gluten-sensitive enteropathy. Lymphocytic gastritis is a histopathological finding with increased CD8+ intraepithelial lymphocytes in children with untreated celiac disease [58, 69]. IPEX syndrome is a systemic disorder characterized by a severe autoimmune enteropathy, insulin-dependent diabetes mellitus, eczema, hematological abnormalities, and eventually other endocrinopathies. The entire gastrointestinal tract can be involved and the gastric mucosa typically shows mild changes such as erythema and mucosal granularity; however, changes can be severe [60]. Histologically, the same inflammatory changes in the stomach are

observed as the small bowel, characterized by a massive mononuclear infiltrate of predominantly T lymphocytes (mainly CD4+), epithelial cell apoptosis, and crypt abscess formation which helps distinguish this immune-mediated enteropathy from other cases of protracted diarrhea and is in contrast to celiac disease with no or only a moderate increase of intraepithelial lymphocytes [61].

It is necessary to screen pediatric patients with organ-specific autoimmune diseases to estimate risk of accumulating coexistent autoimmune diseases, including autoimmune hepatitis, gastritis, type 1 diabetes, and especially autoimmune thyroiditis. Early detection of antibodies by screening at diagnosis of T1DM and regularly thereafter is advocated to take appropriate action to avoid morbidity of disease.

Other Endocrine Conditions

Zollinger-Ellison (ZE) syndrome is a rare condition characterised by a triad of severe ulcer disease, gastric acid hypersecretion, and a gastrinoma, which is usually found in the pancreas, but may be gastric or duodenal origin. ZE may be sporadic or occur in multiple endocrine neoplasia type I (MEN1)/(ZE) and, along with atrophic gastritis and pernicious anemia, is a chronic hypergastrinemic state, where the proliferative effects of gastrin on gastric enterochromaffin (ECL cells) can result in hyperplasia, dysplasia, and finally gastric carcinoid (ECL cell tumors) [62].

Patients with MEN1 develop parathyroid hyperplasia (causing hyperparathyroidism) and pancreatic endocrine tumors (PETs) as well as pituitary and adrenal adenomas.

Vascular Lesions

Hereditary hemorrhagic telangiectasia (HHT) is characterized by the presence of multiple arteriovenous malformations. Although infants are occasionally severely affected, the diagnosis usually suspected during adolescence or later with recurrent anemia because of epistaxis or gastrointestinal bleeding in relation to telangiectases in the stomach or small bowel. Initial clinical signs of HHT may be subtle; however early interventional treatment can prevent life-threatening complications of arteriovenous malformations. Accessible lesions in the stomach are suitable for treatment with endoscopic argon plasma coagulation. In severe anemia and minimal epistaxis or moderate anemia but overt gastrointestinal bleeding, capsule endoscopy [63] detected gastric and small bowel telangiectasia in adults. Recently, a combined syndrome of hereditary hemorrhagic telangiectasia (HHT) and juvenile polyposis syndrome (JPS) was described due to mutations in the SMAD4 gene [64]. JPS is an autosomal dominant condition characterized by multiple juvenile polyps in the gastrointestinal tract with a lifetime cancer risk of 39 %.

In the congenital blue rubber nevus syndrome, multiple giant cutaneous and gastrointestinal venous malformations are associated with intestinal hemorrhage and iron-deficiency anemia. Lesions occur in the esophagus, stomach, duodenum, and colon. Systemic complications include thrombosis and calcification, as well as consumptive coagulopathy and thrombocytopenia [65]. Endoscopy is the technique for diagnosis and also allows immediate therapeutic measures such as argon plasma coagulation, laser photocoagulation, sclerotherapy, or band ligation. In addition, pharmacological treatments based on corticosteroids, interferon-α, vincristine, or octreotide have been described [66].

Portal Hypertensive Gastropathy

Portal hypertensive gastropathy is commonly observed in children with portal hypertension [67]. Children with biliary atresia, the most common cause of childhood cirrhosis, have a high risk of portal hypertension in the first year of life which presents with chronic or acute bleeding. Upper gastrointestinal endoscopy is undertaken when there are clinical or ultrasonic signs of portal hypertension to determine the presence and size of gastroesophageal varices. Characteristic endoscopic mucosal appearances are a mosaic-

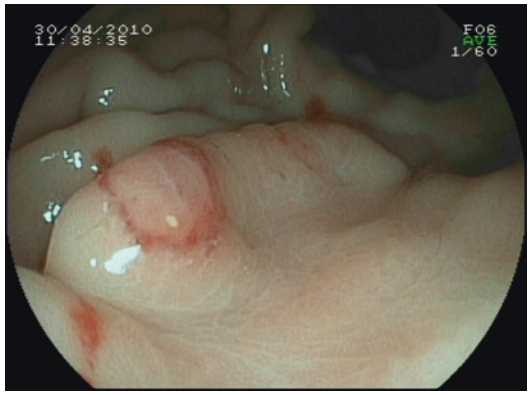

Fig. 126.6 Portal hypertensive gastropathy. Mosaic-like appearance of gastric mucosa with red marks secondary to intramural bleeding in child with biliary atresia

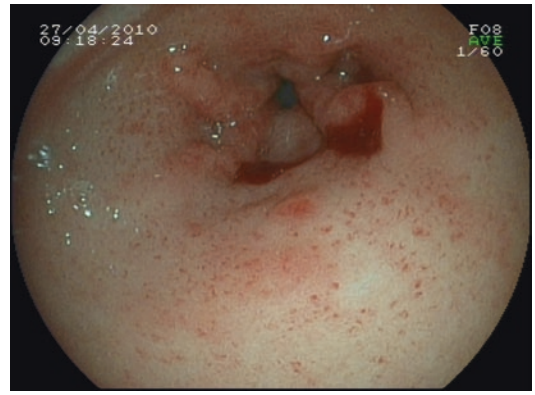

Fig. 126.7 Hemorrhagic renal gastropathy with multiple erosions. Gastric antrum in child with chronic renal failure and painless upper gastrointestinal hemorrhage

like pattern of the gastric mucosa and cherry-red spots or red marks are often seen in severe portal hypertensive gastropathy (Fig. 126.6). Mucosal biopsies carry a risk of bleeding, so are not usually performed; however, histologically, dilation of the mucosal and submucosal capillaries and venules without inflammation is evident. A combination of esophageal varices, red markings, and gastric varices along the cardia is independent factors associated with bleeding and children should receive primary prophylaxis of bleeding, with modalities such as variceal banding, local injection therapy, TIPS, shunt surgery, and liver transplantation [68].

Miscellaneous Conditions

Renal Gastropathy

Feeding problems, anorexia, and vomiting are common in infants and children with chronic renal failure (CRF) and play a major role in the growth failure often found in this condition. Although dyspepsia and upper gastrointestinal bleeding with gastric erosions, antral gastritis, and/or ulcers appear to be relatively rare in children with renal failure compared to adults, symptoms have been reported in 40 % of children with CRF [69]. Hemorrhagic gastropathy is most common, while peptic ulcers are atypical but are likely to be painless and present with bleeding (Figs. 126.7 and 126.8). Mechanisms are multifactorial and may involve a complex disorder of gastrointestinal motility related to reduce renal clearance of hormones such as gastrin, cholecystokinin, and autonomic nervous system dysfunction secondary to uremia and acidosis [70]. Cystinosis is an autosomal recessive condition with multiorgan involvement, particularly renal damage, due to deposition of cystine crystals. Gastrointestinal symptoms may relate to cystine deposits or secondary to treatment with cysteamine (Cystagon TM) treatment, an agent which lowers intracellular cystine and reduces the rate of development of thyroid failure, progression of end-stage renal failure, and the need for transplant in children, as well as improving growth potential [71]. Cysteamine causes hypergastrinemia and ulcers; hence symptoms in affected children are often acid mediated and improve with omeprazole.

Cardiac Disease and Critical Illness

Abdominal pain and vomiting with gastritis can be the sole manifestation of myocarditis and a cardiac cause for vomiting should be considered if hypotension is refractory to rehydration therapy [72]. Gastroesophageal reflux and dysmotility are common in children with congenital

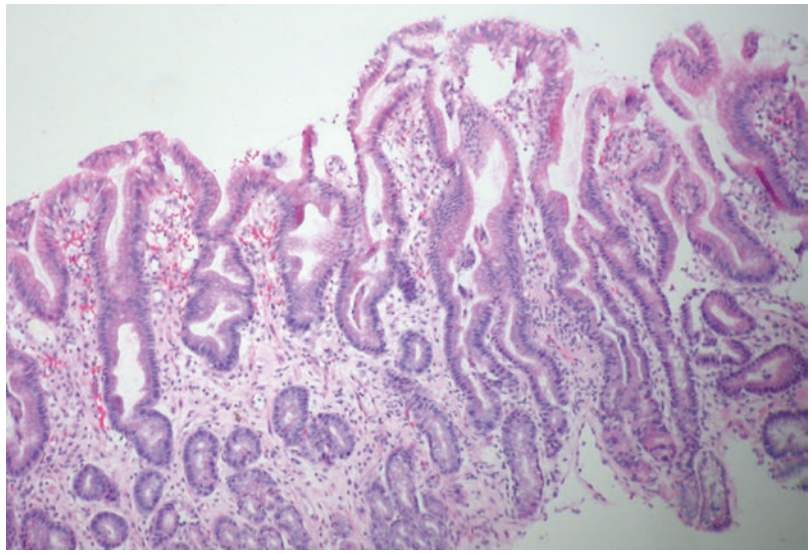

Fig. 126.8 Renal gastropathy. Chronic inflammation with reactive changes without *H.pylori* infection. Mild increase in cellularity, focal hemorrhage, telangiectasia, and foveolar hyperplasia (H&E ×4)

cardiac disease [73]. Critically ill children, including preterm infants who experience severe physiological stress such as respiratory failure, hepatic failure, multiorgan failure, sepsis, head injury, hypotension, trauma, burns, and the use of corticosteroids, are at risk of developing stress-related mucosal disease of the stomach and bleeding. Patients at high risk of stress-related bleeding should receive acid suppression.

Motor Disorders of the Stomach

Gastrointestinal motor dysfunction may result from disorders at every anatomic level of extrinsic innervation. A number of systemic diseases are associated with motility disorders of the stomach (Table 126.5) that interfere with both the normal receptive function (where the proximal stomach relaxes to accommodate a meal) and the propulsive function (where gastric contents are emptied into the pylorus by forceful gastric contractions coordinated with contractions of the duodenum) [74].

When delayed gastric emptying occurs in the absence of mechanical obstruction, the term idiopathic gastroparesis is used. The motor mechanisms associated with gastroparesis are not completely understood, but may involve degenerative myopathic (smooth muscle) or neuropathic processes, where involvement of the autonomic system is the relevant mechanism and gastric enteric neurons, and/or interstitial cells of Cajal may be affected.

Vomiting is common in children with disorders of the central nervous system (CNS) such as cerebral palsy. This is usually ascribed to gastroesophageal reflux (GER), but may represent a wider problem of foregut dysmotility related to abnormal modulation of the enteric nervous system (ENS) by the CNS or to involvement of the enteric nervous system by the same process affecting the brain [75]. Following fundoplication, many patients with CNS disorders continue to have symptoms possibly related to gastric dysrhythmias, the effects of which may be unmasked by fundoplication.

Conditions Associated with Gastroparesis

Down's syndrome (DS) is the most common chromosomal abnormality and up to 77 % of DS children have associated gastrointestinal abnormalities, which may be structural or functional in nature. This suggests that developmental disor-

Table 126.5 Systemic disease and gastroparesis

Systemic causes of gastroparesis	
Prematurity	
Postsurgical	Vagotomy post fundoplication
Postviral	
Metabolic/electrolyte disturbance	Hypokalemia
	Acidosis
	Hypothyroidism
Drug induced	Opioids, anticholinergics
Neuronal dysfunction	
Central nervous system lesions	Cerebral palsy, spinal cord injury
Autonomic nervous system dysfunction	Diabetes mellitus
	Familial dysautonomia
	Guillain-Barré syndrome
Syndromes	Down's syndrome, Rett's syndrome. Noonan's syndrome
Connective tissue disorders/primary smooth muscle disease	Scleroderma, dermatomyositis, SLE, muscular dystrophy
Allergic and eosinophilic gastroenteropathy	Cow's milk protein intolerance
Mitochondrial disorders	
Cardiac and renal disease	

ders of the ENS are probably fundamental to the functional gastrointestinal disturbances encountered in patients with DS [76]. Feeding abnormalities have been reported in female patients with Rett's syndrome [77]. Oropharyngeal dysfunction and gastric dysmotility including diminished peristalsis or atony were apparent on videofluoroscopy. Children may warrant early diagnostic evaluation and intervention strategies to improve nutritional status. Delayed gastric emptying commonly occurs in preterm infants with immaturity of the gastrointestinal tract. Noonan's syndrome is a common dysmorphic syndrome in which failure to thrive and gastrointestinal symptoms are frequent. Electrogastrography (EGG) showed fasting frequency gradient loss along the stomach fundus and pylorus with antral postprandial frequency loss, reminiscent of 32–35-week preterm patterns [78]. Feeding problems appear to be the result of delayed gastrointestinal motor development and resolve as gut motility matures. Symptoms of dyspepsia, nausea, or vomiting observed in hypothyroidism usually resolve with treatment of the thyroid disease [79]. In children with insulin-dependent diabetes mellitus complicated by dyspeptic symptoms and gastroparesis, domperidone is superior to cisapride in reversing gastric emptying delay and gastric electrical abnormalities, as well as in improving dyspeptic symptoms and diabetic metabolic control [80]. The mechanisms involved include autonomic neuropathy, acute hyperglycemia, and abnormalities in gastrointestinal hormones and neuropeptides. Dysmotility of the upper gastrointestinal tract has been reported in children with Hirschsprung's disease. Adult patients with Hirschsprung's disease have an abnormal pattern of gastric emptying, indicating persisting involvement of the upper gastrointestinal tract [81]. Gastric dysmotility is commonly reported in patients with cystic fibrosis [82, 83]. Real-time ultrasonography has demonstrated significantly prolonged gastric emptying time and reduced antral distension in patients with CF and that H2 receptor blockers are more effective than prokinetics in improving dyspeptic symptoms and gastric emptying and distention [84].

Gastroparesis may develop in apparently health children and the symptoms may be preceded by flu-like illness or rotavirus infection [85]. Gastric emptying was delayed in children with acquired gastroparesis evaluated with scintigraphy, and antroduodenal manometry confirmed postprandial antral hypomotility. All children recovered within 6–24 months. A number of other infectious organisms have

been reported to cause gastroparesis including Epstein-Barr virus and varicella and may be seen in autonomic nervous system dysfunction of Guillain-Barré syndrome.

Mitochondrial Disease/Cyclical Vomiting

Mitochondrial disorders usually present with neurological symptoms or myopathic features. Although gastroparesis may occur as part of a mitochondrial disorder, only in a minority are they an early sign [86]. Abnormalities in gastrointestinal motility were reported as an early presenting sign of disorder of the mitochondrial electron transport chain enzymes of oxidative phosphorylation (OXPHOS) [87]. Mitochondrial dysfunction and disease-associated mitochondrial deoxyribonucleic acid sequence variants are believed to be present in most cyclic vomiting syndrome cases; these variants are rarely identifiable on "standard" mitochondrial deoxyribonucleic acid testing. Variants of cyclical vomiting have been reported in Kearns-Sayre syndrome [88].

Complex regional pain syndrome type I (CRPS-I), previously known as reflex sympathetic dystrophy (RSD), is characterized by gastrointestinal dysmotility, migraine, cyclic vomiting and chronic fatigue, abnormally intense and prolonged pain, allodynia, and autonomic nervous system changes (i.e., swelling, skin color and temperature changes, and altered perspiration) that usually appear following a "noxious" trigger such as trauma or surgery. Maternally inherited mitochondrial disease may be a cause CRPS-I, especially in children who present with other manifestations of dysautonomia [89]. Familial dysautonomia (FD) is an autosomal recessive disorder characterized by autonomic and sensory neuropathy, affecting the ocular, gastrointestinal, pulmonary, orthopedic, vasomotor, and neurologic systems. Lack of tears and sweating, orthostatic hypotension, and internuclear ophthalmoplegia are characteristic. The gastrointestinal problems include dysphagia, gastroesophageal dysmotility, gastroesophageal reflux, constipation, and vomiting crises [90, 91]. Maintenance of satisfactory nutrition and quality of life may be a challenge in patients with persistent or progressive gastroparesis. Gastrojejunostomy or jejunostomy may be the treatment of choice [92].

Disorders Affecting Gastroduodenal Smooth Muscle

Systemic Sclerosis

Upper gastrointestinal endoscopy in patients with systemic sclerosis without symptoms of gastrointestinal tract involvement reveals reflux esophagitis and gastritis in the majority of patients [93]. Dysmotility appears to be due to accumulation of extracellular matrix in the submucosa and muscularis that gives thicker gastric antral wall as visualized by endoscopic ultrasound (EUS) of the esophagus [94]. Abnormal gastric emptying has been identified in patients with polymyositis or dermatomyositis but is seldom symptomatic.

Myotonic and Muscular Dystrophy

Myotonic dystrophy is associated with dysmotility which has considered to be due to esophageal rather than gastric dysmotility. However, gastric emptying may be abnormally delayed in myotonic dystrophy patients, even in absence of dyspeptic symptoms [95]. Although muscular dystrophy (MD) (including Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD)) affects primarily striated muscles, smooth muscle cells of the gastrointestinal tract may also be involved. Gastric emptying was reduced in children early in the course of the disease, when gastrointestinal symptoms are absent and skeletal muscle symptoms are minimal [96]. Gastric volvulus is an uncommon condition in the pediatric age group. The cause of gastric volvulus may be idiopathic or secondary to a congenital condition and has been reported due to ligamentous laxity in Ehlers-Danlos syndrome (EDS). These are a heterogeneous group of inherited connective tissue disorders characterized clinically by skin fragility, skin hyperextensibility, joint hypermobility, and excessive bruising. Recent advances in the molecular analysis of EDS have identified defects responsible for EDS

such mutations in the collagen genes I and IV [97, 98].

Spinal muscular atrophy is a neurodegenerative disease that requires multidisciplinary medical care [99]. Weakness may affect several organ systems: respiratory, due to restrictive lung disease; gastrointestinal, in terms of dysphagia and constipation; and orthopedic, with progressive deformities Progressive respiratory muscle weakness with bulbar involvement is the main cause of morbidity and mortality in type I and severe type II spinal muscular atrophy. Since noninvasive positive-pressure ventilation techniques allow longer survival, gut motility problems are emerging that may be challenging to manage [100].

Management of Gastroparesis

The main goals of treatment for gastroparesis are to alleviate symptoms, to maintain adequate fluids and nutrition, and to resume sufficient oral intake of liquids and solids. Intake may be modified to provide small-volume, low-fat, low-fiber liquid nutrition. If dysmotility is progressive continuous rate, enteral gastric feeds are often necessary and jejunal feeds or parenteral nutrition in the presence of foregut dysmotility. Prokinetic drugs such as metoclopramide, erythromycin, and the selective 5-HT4 agonist tegaserod are used to improve gastric motility. Ondansetron and alimemazine may be used when nausea and retching are debilitating symptoms [104]. Surgical procedures such as fundoplication, placement of gastrostomy or gastrojejunostomy feeding tubes [100], gastric electrical stimulation [110 Hyman P], or botulinum toxin A injected into the pyloric sphincter [105] are employed for patients with chronic intractable nausea and vomiting secondary to gastroparesis unresponsive to dietary and medical treatment.

Allergic Disorders

Allergic gastrointestinal motility disorders are common in infancy and early childhood. Cow's milk protein allergy may present with a range of motility problems including gastroesophageal reflux and gastric dysrhythmia/delayed gastric emptying [101]. The exact mechanisms of delayed-onset allergy in motility disorders are being unraveled with a focus on interaction of inflammatory cells such as mast cells and eosinophils with the enteric nervous system [102]. In the human stomach, studies have demonstrated that mast cells degranulate minutes after cow's milk exposure, with associated disruption of normal gastric peristalsis [102]. The ability of the stomach to distend and contract rhythmically is reduced which manifest as inability to accommodate large volumes and delayed gastric emptying [103]. Complete exclusion of the causative antigen, cow's milk with replacement with a partially hydrolyzed, or amino acid formula is recommended.

Gastric Neoplasia

Gastric polyps may represent an underappreciated clinical abnormality in Menke's disease. An infant with Menke's disease presented with gastrointestinal bleeding from solitary gastric polyps. Histopathologic examinations showed submucosal vascular ectasia with mucosal hyperplasia, edema, and ulceration [106]. Hyperplastic esophagogastric polyps occur in the context of neurofibromatosis type 1 (NF-1) [107]. Histologically these polyps show hyperplastic gastric foveolar and/or squamous epithelium with inflamed stroma. Familial adenomatous polyposis (FAP) is the most common inherited polyposis syndrome characterized by the development of hundreds of colorectal adenomatous polyps [109]. 50% had gastric fundal gland polyposis, hamartomatous gastric polyps, and Peutz-Jeghers syndrome (PJS), e.g. in a 2-year-old with STK11 gene, illustrating the importance of considering early screening, along with close clinical review for detection of complications [108].

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Mucosa-Related Gastropathology: The Upper Gastrointestinal Tract and the Microbiome

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Doron D. Kahana and Timothy Van Natta

Extending Our View of Self

Microbiome in Health and Disease

Over the past two decades, we have learned a lot about the biological continuum of life. New molecular techniques allow the detection of microbial DNA in organs that were previously deemed uninhabitable, such as the esophagus and stomach. Many bacteria are fastidious, slow growing, and difficult to cultivate, and thus prior studies overlooked a large number of bacteria. Advancement in genomic analysis of bacterial 16S ribosomal DNA (rDNA) by high-throughput pyrosequencing technique has opened the door to the detection of thousands of microbial species living within us, providing a new perspective on our place in the universe. Turns out, our health is dependent not only on the health of human cells but also the health of the sum collection of all microorganisms living within our body, otherwise called the *microbiome*. With this understanding, a new *germ theory* of disease has emerged, one where disease is not secondary to a single, specific microbe, but rather to the interaction and crosstalk between microbes and their host organism.

The classic germ theory of disease, initially developed by Robert Koch in the nineteenth century, described an infectious disease as the direct consequence of a single pathogen (e.g., tuberculosis, anthrax, HIV) [1]. The new germ theory of disease denotes a process of an aberrant microbial community triggering a host immune response, resulting in inflammation and consequent tissue damage (e.g., IBD, diabetes, heart disease, cancer) [2]. This new theory of disease requires that we further our understanding of the symbiotic relationship between microbes and humans as commensals and hosts.

The microbiome is the aggregate biological load of our entity, more prokaryotic than eukaryotic, with microbial cells outnumbering our own by about tenfold. Microbial genes (*metagenome*) outnumber human genes by two orders of magnitude. Thus, we can consider ourselves as a composite of many creatures, with a genome that is an amalgam of many more than just human genes. The microbiome endows our bodies with physiologic capacities that evolution did not bestow upon us; the symbiotic relationship between our body and microbes forms a barrier that protects us from invaders and maintains homeostatic balance with our environment. Commensal bacteria partake in many immunological tasks, such as induction of oral tolerance, training of the adaptive immune system, and stimulation of mucosal products, including

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secretory immunoglobulin (Ig) A. A state of normal microbial communities is termed *eubiosis* and of abnormal communities is termed *dysbiosis*.

The human gastrointestinal (GI) tract is predominantly a bacterial ecosystem, although archaea, yeast, protozoa, viruses, and parasites may be found. Microbial cell densities in the colon are the highest recorded for any known ecosystem (10^{11}–10^{12}/ml contents). The vast majority of the phylotypes belong to two divisions of bacteria—*Bacteroidetes* (48 %) and *Firmicutes* (51 %). *Proteobacteria*, *Verrucomicrobia*, *Fusobacteria*, *Cyanobacteria*, and *Spirochaetes*, among others, share the remaining 1 %. The stomach and duodenum harbor lower numbers of microorganisms, typically less than 10^3 bacterial cells per gram, as acid, bile, and pancreatic secretions kill most ingested microbes; moreover, propulsive motor activity in the intestine (i.e., migrating motor complex, MMC) impedes colonization of the lumen. A progressive increase in numbers of bacteria is normal along the jejunum and ileum, from approximately 10^4 per gram of intestinal contents proximally to 10^7 distally, with a predominance of Gram-negative aerobes. This is in contrast to the colonic predominance of obligate anaerobes such as *Clostridia* and *Bacteroides*, which are adept at metabolizing proteins, producing short-chain fatty acids (SCFA) and excreting toxins, such as ammonia, amines, and phenols. The putrefaction of proteins is associated with several disease mechanisms, most notably the pathogenesis of hepatic encephalopathy in patients with liver failure, treatment of which is often mediated via modulation of the enteric flora (i.e., with antibiotics, prebiotics, and probiotics) [3].

Several other disorders are directly associated with changes in the composition and/or metabolic function of the enteric flora [4, 5]. Perhaps the most clinically demonstrable entities are antibiotic-associated diarrhea and *Clostridium difficile* colitis. Other disease states are indirectly related to changes in the intestinal ecology; notably, the initiation of colon cancer may occur through microbial production of by-products that act as carcinogens and pro-carcinogens (e.g., indoles, nitrites). High consumption of fat and red meat, particularly processed and cured meat, is believed to trigger the genetic mechanism of colorectal cancer, while consumption of fruits and vegetables, whole grain cereals, fish, and calcium is associated with reduced risk [6]. Dietary and genetic factors interact through the microbiome and influence carcinogenesis via modulation of the metabolic activity of colonocytes [7].

Microbiota and Inflammation

Much of our current understanding of the function of the microbiome comes from studies of *gnotobiotic* animal models, such as mice. The word "gnotobiotic" stems from the Greek words "gnosis" and "bios," meaning "known life"; gnotobiotic animals are reared in a germ-free (GF) laboratory environment and introduced a defined microbiota for experimental reasons. Comparison of GF and normal mice has shown that intestinal microbiota help regulate host energy homeostasis [8]. Some microbes are more efficient at extracting energy from indigestible components of our diet, namely, *fiber* such as cellulose, resistant starch, oligosaccharides, and various glycoproteins. Obesity, for example, has been associated with an increased number of colonic *Firmicutes*, which are particularly efficient in extracting calories from food [9]. By-products of carbohydrate fermentation, specifically short-chain fatty acids (e.g., butyrate, acetate, propionate) and carboxylic acids (e.g., lactic acid), are metabolized on the mucosal level and in the liver and are capable of salvaging several hundreds of calories per day in a healthy human colon [10, 11]. Microbiota can synthesize molecules that are used by their host as nutrients, such as quinones (vitamin K), niacin, biotin, pantothenic acid, folic acid, and cyanocobalamins (vitamin B12) [12]. They also metabolize *xenobiotics*, which are synthetic chemicals, such as antibiotics and other drugs, influencing their bioavailability and contributing to their steady-state metabolism. Lastly, microbiota impact enterocytes and colonocytes directly, through an intricate and evolutionarily conserved

manner, affecting gene expression of various proteins (e.g., nutrient transporters, mucoid glycoproteins) [13, 14].

It is no surprise that an aberrant microbiota, or *dysbiosis*, can induce disease. Dysbiosis can manifest as the colonization of a single, potential pathogen, such as *Helicobacter pylori* or *C. difficile*, which can become virulent and predispose the host to inflammation and disease. Dysbiosis can also manifest as an aberrant ecology that lacks diversity or *mutualism*, such as in the case of inflammatory bowel disease (IBD), in which the inflammatory response is exaggerated and dysregulated toward an aberrant community of microbes, and not just a single pathogen [15]. In Crohn's disease (CD) and ulcerative colitis (UC), mucosal T lymphocytes are believed to overreact against antigens that are commonly found on commensal bacteria and yeast, such as the outer membrane protein C (Omp-C) of *E. coli* and the flagella component CBir-1. Patients with IBD have a measurable alteration in their bacterial communities compared to healthy controls, and the loss of oral tolerance to a range of dietary antigens is strongly implicated in aggravating of the disease [16]. Gut microbiota are believed to invoke other medical conditions beyond IBD, such as diabetes mellitus, rheumatoid arthritis, asthma, and cardiovascular disease [17].

Intestinal microbiota interact with mucosal epithelial cells in a fashion that creates crosstalk between luminal contents and host innate and adaptive immune responses [18, 19]. Mutualism between host and commensals is vital to health, with activation of innate host defense mechanisms resulting in end-organ inflammation and damage. On the molecular level, our immune system recognizes and engages conserved molecular patterns in the environment via *pattern-recognition receptors* (PRR), such as Toll-like receptors (TLR) and nucleotide-binding oligomerization domain (NOD) receptors. PRR have been shown to be extremely important in mediating inflammation and repair [20]. They converge signals that result in regulation of transcription factors, such as nuclear factor-kappa B (NF-kB), which regulate the transcription of genes responsible for the synthesis of inflammatory molecules (e.g., tumor necrosis factor, cytokines, leukotrienes). Intestinal cells express PRR and thus can function as antigen-presenting cells, activating innate immunity. And so the entire intestinal epithelial layer is an immune organ, alive with bacteria feasting on food matter, other bacteria, or their host. It is only natural for a host to evolve toward mutualism with its microbiome.

Microbial impact on the immune system is mediated via organized lymphoid structures within the small intestinal mucosa—the gut-associated lymphoid tissue (GALT). GF animals have been shown to have low density of GALT and low levels of circulating Ig [21]. Following exposure to microbes, the number of mucosal lymphocytes expands, germinal centers and Ig-producing cells appear, and there is a significant increase in serum Ig levels. Commensal bacteria elicit a different cytokine response than pathogenic bacteria, involving induction of regulatory pathways of the immune system (e.g., transforming growth factor (TGF)-β and interleukin (IL)-10) [22]. For example, *Lactobacillus* strains have been shown to downregulate the spontaneous release of tumor necrosis factor alpha (TNF-α) by inflamed tissue and balance the inflammatory response induced by *Escherichia coli* [23]. It is now known that mutualism helps shape host cellular differentiation and proliferation, especially on the epithelial layer. Mucosal injury, for example, is further sustained in the absence of bacteria or with disruption of the communication channel, as noted in TLR-4 knockout mice models of IBD [24].

Further evidence supports the vital role of microbes in the development and balance of the immune system. An important example is embodied by the *hygiene hypothesis*, which claims that the increased incidence of allergy and immune-mediated diseases noted in Westernized societies may, to some extent, be explained by aberrant microbial exposure early in life [25, 26]. The hypothesis suggests that inability to form mutualism between host and microbes can lead to a maldeveloped immune system showing exaggerated immune responses, such as with asthma, atopic dermatitis, allergic rhinitis, multiple sclerosis, and others. The hygiene hypothesis is supported

by epidemiological studies noting lower allergy and asthma rates in developing countries relative to their developed counterparts. Moreover, therapeutic benefit with the use of probiotics to treat atopic disease has been reported [27]. And although the evidence is circumstantial and does not prove causation, animal data is more convincing of an immune dysregulatory link.

In summary, we must extend our view of self beyond human cells, even beyond human genes, and include the vast microbial world that engulfs our body. Its relation to health and disease is a new concept in the evolution of medicine, and we must consider the effects our biology and environment have on a delicate symbiotic balance.

Microbiota of the Esophagus and Stomach

Reflux Esophagitis and Barrett Esophagus

The anatomic junction between the distal esophagus and stomach endures the constant threat of gastric content reflux. Stomach contents are corrosive and can cause inflammatory changes in the stratified squamous epithelium of the esophagus, including hyperplasia of the basal layer and necrotic erosions. The correlation between gastric reflux and esophageal adenocarcinoma is clinically supported by the observed increased incidence of both the cancer and gastroesophageal reflux disease (GERD). Since the 1970s, we have witnessed a sixfold increase in the incidence of esophageal cancer following a similar increase rate in the prevalence of GERD [28–30]. Barrett esophagus (BE), considered to be the precursor condition to esophageal adenocarcinoma, is found in up to 12 % of patients undergoing endoscopy for symptoms of GERD [31, 32]. And although all cases of adenocarcinoma are believed to be preceded by BE, only 5 % of patients with BE appear to develop adenocarcinoma [33].

Recent studies have shown that up to 100 different commensal bacterial species may reside in the normal distal esophagus at any given time [34]. Similar to the rest of the gut, members of at least five phyla are represented: *Firmicutes* (majority), *Bacteroidetes* (second most common), *Actinobacteria*, *Proteobacteria*, and *Fusobacteria* (Table 127.1). Other phyla, such as *Spirochaetes* and *Deferribacteres*, are present in the oral cavity but not commonly identified in the distal esophagus, indicating that environmental conditions are different in the two anatomical areas. Although molecular detection technique cannot distinguish colonizing or living bacteria from naked bacterial genomes, studies suggest that the esophageal microbiota is a relatively stable and unique community and not merely composed of organisms in transit.

The presence of *H. pylori* in esophageal samples of some patients with GERD confirms that gastric bacteria can be brought into the distal esophagus by reflux. *H. pylori* colonization of the esophagus is less likely, so its presence is believed to be migratory. Several studies of patients with BE report prominent changes in ecological communities of the esophagus relative to normal controls [36, 38, 39]. Patients with BE are known to have a high prevalence of esophageal motility disturbances, and weak LES pressure and poor contractility contribute to GERD and delayed clearance of refluxate [35]. These motility disturbances may predispose to bacterial overgrowth in the distal esophagus, leading to further disturbance of the LES and further increase of reflux; thus, a positive-feedback loop is formed, between reflux and mucosal injury.

Yang et al. conducted a study of patients with GERD and BE compared to controls and classified the esophageal microbial community into two enterotypes: type 1 was rich in facultative anaerobic Gram-positive *Firmicutes*, especially *Streptococcus* phylotypes (79 %); type 2 was composed of only 30 % *Streptococcus* and was characterized by a greater number of obligate anaerobes, such as *Bacteroidetes* phylotypes (e.g., *Prevotella* 13 %) and Gram-negative *Proteobacteria* (e.g., *Haemophilus* 6 %, *Neisseria* 5 %). Enterotype II microbial community showed a significant association with GERD (odds ratio, OR >15) [36] (Fig. 127.1). The authors conclude that enterotype 2 microbiota might play a causative role in GERD. They argue that abnormal

Table 127.1 Bacterial phyla with examples of commensal and pathogenic genera and species

Firmicutes	Bacteroidetes	Actinobacteria	Proteobacteria	Fusobacteria
Bacillus *Listeria* *Staphylococcus* *Streptococcus* *Enterococcus* *Lactobacillus* *Clostridium* *Heliobacterium* *Mycoplasma*	*Bacteroides* *Flavobacterium* *Sphingobacterium*	*Bifidobacterium* *Mycobacterium* *Corynebacterium* *Streptomyces*	*Escherichia coli* *Enterobacterium* *Haemophilus* *Pseudomonas* *Neisseria* *Campylobacter* *Aeromonas*	*Fusobacterium nucleatum* *F. necrophorum* *F. russii*

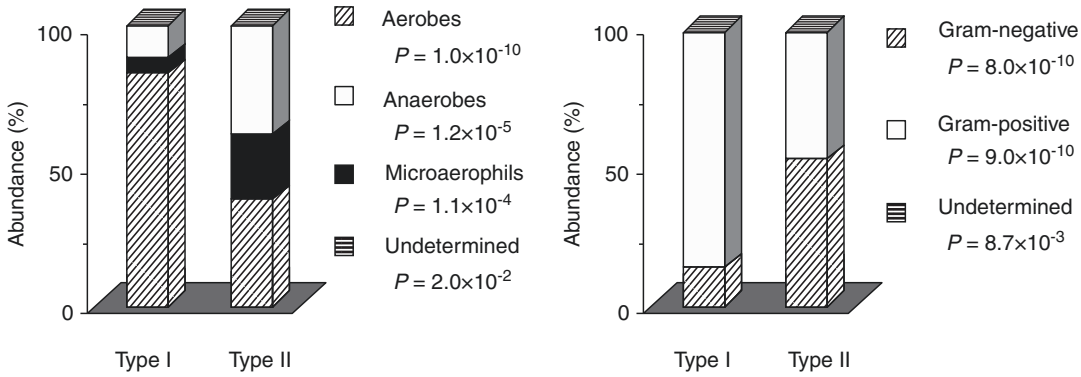

Fig. 127.1 Taxonomic characterization of esophageal microbiota by population of main bacterial groups. *Left:* comparisons of microbiota types according to culture conditions. *Right:* comparisons of microbiota types according to staining properties (Adapted with permission from Yang et al. [36])

lower esophageal sphincter (LES) pressure and esophageal acidification during transient LES relaxation are critical and that the etiology of abnormal LES function is incompletely understood and might actually stem from esophageal dysbiosis [37].

Macfarlane et al. corroborated the above finding and also identified bacterial species that produce nitrosamines in patients with BE [38]. The authors provided evidence to support the hypothetical correlation between the presence of bacteria that promote nitrosamine production and consequent tissue metaplasia and dysplasia. Esophageal biopsies and aspirates were collected from 14 individuals, 7 with known BE and 7 without BE but with upper GI symptoms. Bacteria were cultivated and measured by PCR, with 46 bacterial species belonging to 16 genera identified; 18 species from 7 subjects without BE and 38 species from 7 patients with BE, and 10 species common to both groups. Similar to the study by Yang, Macfarlane found that the normal esophageal community consists of a majority of lactobacilli and streptococci (*Firmicutes*) and that patients with BE had higher counts of Gram-negative anaerobic bacteria, such as *Prevotella* (*Bacteroidetes*) and *Neisseria* (*Proteobacteria*). Lactobacilli were only detected in mucosal samples from the control group; conversely, *Fusobacterium*, *Megasphaera*, *Neisseria*, and *Campylobacter* species were only detected in patients with BE. Interestingly, yeast (e.g., *Candida* and *Saccharomyces*) were found in aspirates from both groups, but only BE patients had yeast present within the mucosa. Moreover, high levels of *Campylobacter* species (*Proteobacteria*), which reduce nitrate and manufacture nitrosamines, were reported to colonize 4 of 7 (57 %) patients with BE and none of the control subjects. *Campylobacter concisus* was

the most prevalent nitrosamine-producing species detected and occurred in the highest numbers.

Osias et al. in a study using only cultivation and staining techniques noted the prominence of *Firmicutes*, specifically streptococcus species, and reported that patients with BE had higher counts of bacteria than non-BE patients [39]. Moreover, an association was measured between progressively higher bacterial count and higher grades of mucosal dysplasia ($P=0.028$). Thus, consistently among the above three studies, there appears to be a putative role for bacteria in the development of chronic inflammation and BE, with progression to dysplasia and cancer.

In summary, patients with BE harbor a unique, mucosal community of bacteria and yeast that is different from control subjects. It is more diverse and contains a higher density of microbes, fewer streptococci and lactobacilli, and other Gram-positive facultative aerobes, and more Gram-negative anaerobic and microaerophilic bacteria, such as *Prevotella*, *Neisseria*, and *Campylobacter*. The capacity of species like *Campylobacter* to produce nitrosamines makes them ideal candidates for pathogenic activity in BE. Nitrate reduction and production of nitrosamines from nitrites and secondary amines, which often exist in the form of protein, can occur only under strongly acidic conditions, which is consistent with the environment of patients with GERD and BE. These chemicals are known to be highly carcinogenic and might be the responsible agents for the disease-to-cancer axis in GERD.

Megaesophagus and Esophageal Atresia

Achalasia of the LES and esophageal motor disturbances, such as in Chagas disease, induce progressive dilatation of the organ, causing megaesophagus and resulting in poor content evacuation and chronic stasis. Stagnated contents provide a medium for bacterial growth, which likely contribute to some of the comorbidities of megaesophagus, such as recurrent aspiration pneumonia and chronic pulmonary infections, as well as infectious complications related to esophageal perforation during surgical or endoscopic procedures [40, 41]. As noted above, bacterial overgrowth is believed to favor development of epithelial dysplasia, the first step in the development of cancer, and indeed cancer is 33 times more frequent in patients with megaesophagus than in the general population [42, 43].

Pajecki et al. conducted a prospective study of the bacterial content of 15 patients with Chagas megaesophageal disease, age range 24–74 years (mean 49.1), and compared them to a control group of 10 patients evaluated by upper endoscopy for general dyspeptic complaints [44]. While both groups showed a predominance of aerobic Gram-positive and anaerobic bacteria, cultures were positive much more frequently on aspirates from diseased esophagus than from controls (93 % vs. 40 %, $p<0.05$). *Streptococcus* (Gram-positive, lactose-fermenting, aerobic Firmicute) appeared in all positive cultures in both groups; *Veillonella* (Gram-negative, anaerobic Firmicute) was identified in 73.3 % of the patients with megaesophagus versus none of the control patients. Concentrations of microbes were 10^1–10^2 in the control group and 10^1–10^5 in the megaesophagus group, with statistical significance observed for specific organisms.

The finding of *Streptococcus* is consistent with other studies of esophageal and oropharyngeal microbiota; thus, it is likely an important component of the microbiota in the esophagus as well as oropharynx. With stasis of contents, as with megaesophagus, swallowed microorganisms proliferate and thrive on stagnant food matter, creating an environment with low oxygen content that is propitious for anaerobic, Gram-negative bacteria, such as *Veillonella*, which is abnormal for the esophagus. It is believed that such colonization predisposes patients to worse respiratory infections due to aspirative phenomena of more harmful anaerobes. This is corroborated by the finding of pulmonary disease in 34 % of patients with Chagas megaesophagus on autopsy [45]. A different study reported a high incidence of *Mycobacterium fortuitum* in a similar cohort of patients [46].

The increased prevalence of esophageal squamous cell carcinoma in patients with Chagas disease may be related to increased concentration of microbial by-products within the esophagus, such as nitrosamine compounds from protein putrefaction, as well as stasis of dietary carcinogens within the esophagus [47].

Data on the microbial composition of patients with esophageal atresia (EA) is extremely sparse. A study by Bayston et al. in 1984 of the fecal flora in neonates with EA is the only available microecological study of patients with EA [48]. It reported that in feces of newborns with EA, culture technique isolated *Staphylococcus albus* (aka *S. epidermis*) most frequently, as well as klebsiella, enterococci, and clostridia. Relevant information for our purposes was that no bifidobacteria were found in fecal cultures or seen on Gram stain until after the neonates received their first feed (which was often delayed and introduced after placement of a gastrostomy tube). Bifidobacteria are an important constituent of the microbiome and the predominant bacteria in nursing infants; data have implicated their importance for immune development and possible prevention of inflammatory and atopic disorders [49, 50]. An important message from Bayston's study is that neonates with EA may not be able to make enteric vitamin K, so an additional dose at 2 or 3 weeks of age was recommended, particularly if further surgery is planned. Interestingly, the authors mentioned the implication of neonatal dysbiosis on immune development, with possible impairment of the opsonization and complement system and increased risk for infectious complications. Moreover, the authors recommended against prophylactic or empiric antibiotics, as these were shown in their study to eradicate the intestinal flora and further delay proper colonization.

Children with EA are now reaching adulthood in larger numbers, and many of them experience functional problems with both GI and respiratory systems after the initial postoperative period [51]. Several series on long-term follow-ups of adolescents and young adults with EA after surgical repair reported persistent respiratory symptoms in a large number of patients, including bronchitis, brassy or chronic cough, pneumonia, and wheezing [52, 53]. Almost a quarter of the children with EA are found to have clinically relevant tracheomalacia; more than two-thirds experience recurrent respiratory tract infections in the first 5 years of life; and about a fourth require prophylactic antibiotics [54]. The morbidity from respiratory disease appears to abate as patients get older, but approximately 40 % of adolescents and 10 % of adults continue to have respiratory symptoms [55, 56]. Wheezing appears to be the most frequent symptom beyond childhood, with 22 % of adolescents and 16 % of adults reporting asthma; airway hyperresponsiveness to histamine is reportedly increased in 40–78 % of patients. Airway remodeling likely contributes to airway obstruction, with an obstructive defect measured in 30–57 % of subjects. However, bronchial biopsies performed in children with EA demonstrated a thickened basal membrane, similar to asthma; thus, both inflammatory processes and intrinsic airway remodeling are likely to contribute to the obstructive phenomenon noted in patients with a history of EA. The role of changes in the microbiome (i.e., the delayed neonatal colonization of bifidobacteria in lieu of delayed feeding) as possible contributor to inflammatory processes has not been investigated.

In summary, megaesophagus and EA are conditions that result in esophageal dysmotility, stasis of food, and propensity for aberrant microbial communities. Patients with megaesophagus are clinically noted to be prone to respiratory infections and esophageal cancer with dysbiosis possibly playing a causal role. Recurrent respiratory infection and other respiratory symptoms, such as cough and wheezing, are also noted in patients with EA. It is unknown whether esophageal stasis and/or dysbiosis contributes to these symptoms, although the delayed colonization of the GI tract due to delayed feeding in these patients is hypothetically an indirect connection.

Gastritis and Gastric Cancer

It is well recognized nowadays that *H. pylori*, a proteobacterium, is a significant player in the human gastric microbial ecosystem. *H. pylori* is

believed to be indigenous to the stomach and has coevolved with humans for at least 50,000 years [57]. In the past, traditional methods for cultivating gastric aspirates or mucosal biopsies have identified firmicutes, proteobacteria, actinobacteria, and fusobacteria, as well as low abundance of yeast. Newer molecular methods have led to data suggesting that *H. pylori* is a common gastric colonizer and recognize a native population of bacteria present in the stomach, normally in low concentrations of 10^1–10^3 CFU/mL. A study by Bik et al. on patients with symptomatic upper GI disease reported the presence of 128 bacterial phylotypes among 8 phyla, with *H. pylori* sequences present in 19 of 23 patients tested; 12 of the 19 also tested positive for *H. pylori* using conventional methods [58]. This latter group demonstrated a relative lack of non-proteobacteria phylotypes, especially bacteroidetes, compared with *H. pylori*-negative subjects, meaning that *H. pylori* and other proteobacteria had become dominant colonizers. The authors conclude that their findings confirm the presence of distinct bacterial communities that have adapted to the specific habitat in the stomach.

These findings were corroborated by Maldonado-Contreras et al. who also reported marked differences in the structure of the gastric bacterial community according to *H. pylori* status [59]. The authors used gene microarray PhyloChip technology to analyze the 16S rRNA of gastric aspirates of 12 immigrant patients from rural Venezuela, South Asia, and Africa and found *H. pylori* in 8 of them. The communities of all subjects were dominated by only four phyla: *Proteobacteria*, *Firmicutes*, *Actinobacteria*, and *Bacteroidetes*. As previously noted, *H. pylori* status was associated with increased abundance of proteobacteria and decreased abundance of actinobacteria, bacteroidetes, and firmicutes. *H. pylori* was found in patients even without GI disease, which is important because it underscores the likelihood that certain bacterial virulence factors or host defense mechanisms are likely responsible for the disease state that follows *H. pylori* infection. Interestingly, not all host response mechanisms to *H. pylori* are pathogenic, and evolutionary advantage may be conferred to colonizers of *H. pylori*, such as protection against tuberculosis [60].

In a molecular profiling study of gastric microbiota in patients with non-*H. pylori* gastritis and without exposure to nonsteroidal anti-inflammatory drugs (NSAID), Li et al. reported that 70.5 % of all microbial clones belonged to five genera, specifically *Streptococcus*, *Prevotella*, *Neisseria*, *Haemophilus*, and *Porphyromonas* [61]. Interestingly, the overall microbial complexity of patients in this study was remarkably similar to the patients in the Bik study, despite vastly different geographic locations and patient ethnicities. Li compared the microbiota of the antrum to that of the body in patients with and without gastritis and concluded that the samples were quite similar. Moreover, cultivation of the same streptococcal phylotypes identified through molecular 16S rRNA sequencing helped the authors conclude that these bacteria are true residents in the stomach mucosa. The question of causality remains, though, as it is unclear whether the increase in streptococcus abundance is causative for non-*H. pylori*, non-NSAID gastritis or secondary to inflammation caused by another trigger. A second unanswered question is whether streptococcus phylotypes predispose the antral mucosa to colonization and invasion by *H. pylori*, which can lead to cancer.

Gastric cancer is a global health concern—the fourth most common cancer and the second leading cause of cancer-related deaths worldwide [62]. Research has shown that *H. pylori* is a major associative agent in gastric cancer, and eradication of *H. pylori* has been shown to decrease the incidence of gastric cancer, although the causative mechanism is still not yet fully understood [63]. In antral-predominant gastritis, the production of gastric acid is increased (i.e., *hyperchlorhydria*), a condition associated with a higher risk of developing duodenal ulcers but believed to be protective against gastric cancer. In contrast, body-predominant gastritis leads to lower production of gastric acid (i.e., *hypochlorhydria*) and may lead to atrophic gastritis, a condition known to increase the risk for gastric cancer. Incidentally, the hypochlorhydic environment has been shown suitable for growth of nitrogen-

reducing bacteria capable of producing carcinogenic nitrosamine compounds. This raises the question of whether bacteria other than *H. pylori* contribute to the development of gastric cancer.

A study by Dicksved et al. looked at ten patients with non-cardiac gastric cancer and five dyspeptic control patients with normal gastric mucosal morphology [64]. Eight out of the ten cancer patients were positive for *H. pylori* by conventional testing (three by culture); none of the controls were positive for *H. pylori*. Analysis by restricted fragment length polymorphism (RFLP) yielded 102 phylotypes of bacteria clustering into the regular phyla of *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Proteobacteria*, and *Fusobacteria*. As in the esophagus, members of the *Firmicutes* were most highly represented, with the majority corresponding to *Streptococcus*, *Lactobacillus*, and different *Clostridia*, such as veillonella. Notably, the study was unable to discern differences in total abundance of bacteria between cancer patients and controls, and no significant differences were measured in diversity indices between these two groups. The authors did suggest that the phylotypes of control patients appeared to be clustered, suggesting that these bacterial communities were more similar to each other than to those of cancer patients. Moreover, cancer patients were separately measured to have significantly different communities from each other. Interestingly, *H. pylori* was only detected in one of the cancer patients. The study did not measure nitrosamine compounds in gastric aspirates or distinguish the presence of nitrate-reducing bacteria, so further conclusions cannot be made. Another major deficit in this study and others is the lack of data on gastric aspirate pH, which might show some correlation with gastric bacterial communities. It is interesting to note that microbial dysbiosis is suggested in other forms of GI cancers, such as colorectal cancer, with significant elevation measured in the population of bacteroides and prevotella [65]. *Bacteroides fragilis*, for example, has been implicated in carcinogenesis due to its ability to produce a metalloprotease that disturbs host immune responses [66].

In summary, studies confirm the presence of distinct bacterial communities residing in the stomach. The role of bacteria in gastritis and cancer is still under scrutiny, and although *H*. pylori is an important player in gastric inflammation and dysplasia, other bacteria, virulence factors, and host response mechanisms are all prime targets for further research.

Consequences of Gastric Acid Suppression

Acid Suppression and Bacterial Overgrowth

Decreased acid secretion predisposes patients to increased bacterial counts in gastric and duodenal fluid. The ability to secrete acid into the stomach evolved secondary to conferred survival advantage for those species that possessed it. Medical acid suppression in humans and experimental animals is not associated with immediate morbidity. Rather, clear clinical benefits are noted with acid suppression therapy for multiple conditions, such as when used in conjunction with antibiotics for eradication of *H. pylori* or to minimize progression of BE [67]. Yet, interrupting the acidic environment in the stomach does appear to carry long-term complications, including bacterial overgrowth and its consequent events, such as increased risk for enteric and non-enteric infections, nutrient malabsorption, and deconjugation of bile acids.

The relationship between gastric pH and gastric bacterial counts is strong, with increased pH directly correlated to increased bacterial concentration in stomach aspirates [68]. Normal gastric pH is in the 1–2 range and associated with median gastric bacterial counts less than 10^3 CFU/ml; as the pH rises above 5–6, bacterial counts reach a plateau of about 10^7 CFU/ml (Fig. 127.2). Gastric acid also influences the composition of the microflora of the small intestine, and early studies on patients with peptic ulcer disease requiring acid-reducing surgery, such as vagotomy or antrectomy, noted jejunal aspirates with an increase in bacterial counts from 10^3 CFU/mL preoperatively to 10^8 postoperatively.

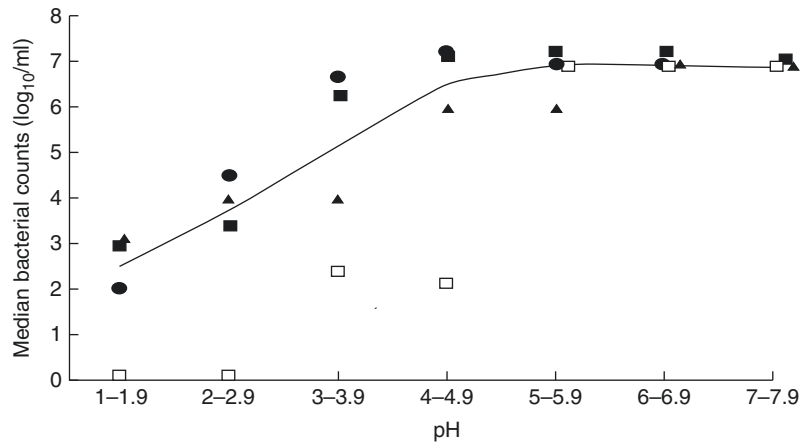

Fig. 127.2 Relationship between gastric luminal pH and bacterial counts in the gastric juice from four studies in which simultaneous measurements of bacterial numbers ad pH were made. The *curve* indicates the median value from the studies at each pH range (Reprinted, with permission, from Yeomans et al. [68])

Discussion of small intestinal bacterial overgrowth (SIBO) is outside the realm of this book, but since some of the more serious complications of gastric acid suppression involve SIBO, a few brief comments are in order. First, aspiration of jejunal fluid and standard cultivation techniques have been the gold standard in diagnosing SIBO, which in the past often failed to produce growth, leading to incorrect conclusions. Justesen et al. reported in a 1984 study on 51 children without gastrointestinal disorders that a consistent population of jejunal microbiota was present in 26 (51 %) of tested subjects. Cultivation of aspirates yielded, in decreasing frequency, growth of *Streptococcus viridans*, *Veillonella parvula*, *Haemophilus parainfluenzae*, lactobacillus, corynebacterium, actinomyces, bacteroides, *Haemophilus influenzae*, neisseria, *Staphylococcus aureus*, and candida [69]. The concentration of growth ranged from $<10^1$ CFU/mL in 37 % of samples (i.e., sterile) to $10^{8–9}$ in one sample, with a median concentration in the range of 10^4–10^6. The growth concentration of the main species isolated was similar for the majority of subjects, from 5.0×10^4 CFU/ml (e.g., lactobacillus) to 2.0×10^3 (e.g., peptococcus).

Today, most definitions of normal small intestinal flora describe population numbers to be $\leq 10^4$ CFU/mL, but certainly greater than normal growth concentrations in the stomach and esophagus. Jejunal aspirates with growth greater than 10^4 are considered abnormal, and the symptomatic patient may be diagnosed with SIBO and treated accordingly [70]. Several host defense mechanisms prevent excessive colonization of the proximal small intestine, including gastric acid and digestive enzyme production, antegrade peristalsis, mucosal protection, and immune factors, such as secretory immunoglobulin (Ig) A. In most patients, SIBO is not caused by a single bacterial strain but rather represents an increase of "normal" communities of bacteria. Select bacteria implicated in SIBO include microaerophilic and facultative anaerobic bacteria that sneak in from the oropharynx, such as streptococcus, *Escherichia coli*, staphylococcus, and klebsiella, as well as resident anaerobes, such as bacteroides, lactobacillus, and clostridium [71]. Recent studies using pyrosequencing methods report that over 50 % of bacterial species in the proximal intestine belong to strains that have yet to be cultivated [72]. Indeed, poor diagnostic correlation has been noted between jejunal aspirate testing, breath testing, and pyrosequencing technique, an observation requiring further study of current definitions and clinical implications of SIBO [73].

The bacterial profile in the small intestine in response to acid suppression is similar to the bacterial profile produced by bacterial overgrowth in the stomach, compromising largely of oropharyngeal flora. SIBO is known to cause deconjugation of bile acids, a process that interferes with digestion and nutrient absorption. A study by Theisen et al. of 30 patients treated with 40 mg of omeprazole for 3 months reported a markedly increased concentration of unconjugated

bile acids in gastric aspirates, in direct correlation with measured bacterial counts [74]. Also, bacteria can produce various toxic molecules that carry systemic adverse effects, such as ammonia, D-lactate, peptidoglycans, and even ethanol. These molecules upregulate systemic inflammation and may contribute to certain clinical conditions (e.g., hepatic encephalopathy, steatohepatitis). Bacterial overgrowth in the small intestine may also impact the morphological structure of the bowel, with associated inflammatory changes and villous atrophy resulting in nutrient malabsorption.

The proton pump inhibitors (PPI) produce profound effects on the production of gastric acid. Although the safety profile for this class of medications has been excellent, studies on the long-term complications of PPI intake are emerging, and they are significant. Specifically, PPI appear to result in malabsorption of nutrients (e.g., iron, calcium), and studies suggest that chronic intake increases the risk for bone disease in older patients (e.g., osteopenia) [75]. Certain micronutrients require an acidic environment for dissolution and conversion to isoforms with increased bioavailability. Calcium disintegration and dissolution, for example, decreases from 96 % at pH 1 to 23 % at pH 6.1. O'Connell et al. conducted a randomized, double-blind, placebo-controlled study on calcium absorption, comparing placebo to omeprazole 20 mg daily for 1 week in a community-dwelling population of women ≥65 years of age. Subjects were given labeled ^{45}Ca at a dose of 500 mg per day, and blood samples were measured at baseline and 5 h after calcium ingestion. Omeprazole was found to markedly decrease fractionated calcium absorption from 9.1 % with placebo to 3.5 % with omeprazole (Fig. 127.3) [76].

Available studies do not show a clear correlation between PPI treatment and increased nitrosamine compounds in gastric fluid, although rising bacterial counts in the stomach are believed to result in increased nitrate-reducing strains (e.g., peptococcus, klebsiella, escherichia, and helicobacter). One study demonstrated increased urinary excretion of nitrosamine compounds in patients on PPI therapy [77]. As already noted, the contribution of nitrosamine formation to gastric cancer is not fully understood, but it is important to mention that cancer rates have increased alongside the increased intake of dietary nitrates (e.g., animal protein) [78].

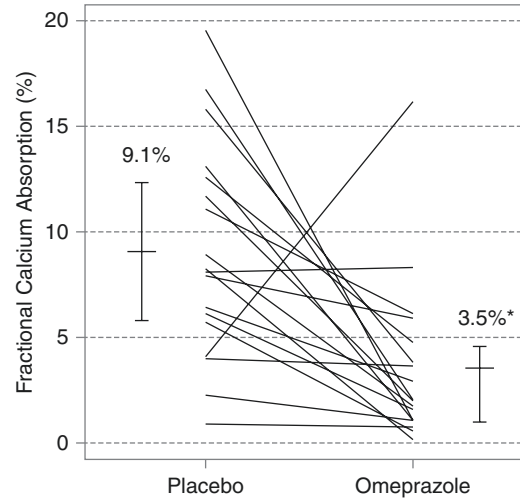

Fig. 127.3 Fractional calcium absorption for each subject ($N=18$) after 1 week of placebo versus omeprazole 20 mg. The 25–75th percentile bars and means are depicted for each treatment period. The difference between placebo and omeprazole was statistically significant, $P=0.003$* (Adapted with permission from O' Connel et al. [78])

Acid Suppression and Risk for Infection

The interplay between bacteria and the chemical milieu of the stomach is strongly implicated in the risk for infections. Many bacteria, such as *Salmonella typhimurium*, a leading cause of gastroenteritis worldwide, cannot survive pH <4; other bacteria, such as *E. coli* 0157:H7, are able to survive a very low pH [79]. Some bacteria have evolved to combat gastric acid, such as *Yersinia enterocolitica* and *H. pylori*, both of which produce a urease enzyme that hydrolyses urea to carbon dioxide and ammonia, producing an ammonia cloud or basic buffer zone around the organism.

Clinical evidence has been slow to accumulate, but data now appear to suggest that PPI

therapy is associated with increased risk for enteric infections, such as salmonella, campylobacter, *Vibrio cholera*, and *C. difficile*. Leonard et al. reviewed 25 studies that included a total of 29,748 patients who received acid suppression therapy and concluded that enteric infection rates were significantly higher than case controls [80]. Specifically, the odds ratio of *C. difficile* infection in patients receiving acid-suppressive drugs was 1.95 (95 % CI 1.48–2.58) times higher on acid suppression versus controls, with a higher risk conferred for PPI over H2-receptor antagonists (H2RA); the odds ratio of acquiring other enteric infections (e.g., salmonella, campylobacter, shigella) was 2.55 (95 % CI 1.53–4.26) times higher than case controls. Dial et al. reported that the incidence of *C. difficile* infection in patients, as documented in the General Practice Research Database in the United Kingdom, increased by an OR of 2.9 (95 % CI 2.4–3.4) with current use of PPI and 2.0 (95 % CI 1.6–2.7) for H2RA [81]. The authors concluded that extra caution should be practiced in caring for those at increased risk for developing enteric infections, such as travelers, hospitalized patients, children, and the elderly.

The risk for non-enteric infections, specifically respiratory infections, is also increased with acid suppression. Hypochlorhydria (pH >4) is an abnormal environment for the stomach, and the bacterial overgrowth that ensues has been shown to cause significant respiratory disease if aspirated. Achlorhydric stomachs contain large numbers of intestinal *coliforms*, rod-shaped Gram-negative bacteria (e.g., citrobacter, enterobacter, klebsiella, serratia, and escherichia), as well as streptococcus and staphylococcus [82]. Studies on PPI use note that the severity of bacterial overgrowth is directly related to the amount of time gastric pH is >4. Therefore, it is possible that clinical benefit may be derived from pulse administration of PPI in asymptomatic patients who can tolerate intermittent dosing (e.g., post-EA repair).

A landmark study by Laheij et al. reviewed the records of 364,683 individuals living in The Netherlands, as part of the Integrated Primary Care Information project, a database study of patient records in primary care setting, and reported that patients taking acid-suppressive drugs developed pneumonia 4.47 (95 % CI 3.82–5.12) times more often compared to those who never used acid-suppressive drugs [83]. The study identified and reviewed 5,551 first occurrences of pneumonia over 7 years; 185 cases occurred in individuals taking acid-suppressive drugs. The adjusted increased relative risk of pneumonia in individuals taking acid-suppressive drugs was 1.27 (95 % CI, 1.06–1.54); the adjusted attributable risk was 42 % for PPI and 37 % for H2RA. Overall, 1.05 pneumonia cases per 100 person-years of PPI exposure and 0.86 pneumonia cases per 100 person-years of H2RA exposure could be attributed directly to the use of acid-suppressive drugs. This roughly translated to one case of pneumonia for every 226 patients treated with PPI and every 508 patients treated with H2RA. A dose response trend was observed in the subgroup of patients taking PPI, consistent with previous studies; this again raises the notion that pulse administration of PPI may have clinical relevance to the risk for infection.

A more recent Danish study by Gulmerz et al. reported that the OR associated with current use of PPI and community-acquired pneumonia was 1.5 (95 % CI 1.3–1.7) relative to case controls. The study reviewed 7,642 cases of community-acquired pneumonia in patients who were discharged from hospital and compared to 34,176 control subjects, matched to age and sex. Initiating PPI therapy showed a strong association with pneumonia with an OR of 5.0 (95 % CI 2.1–11.7) [84]. Other studies have corroborated this correlation, but to a different extent and some with skepticism. A meta-analysis by Johnstone et al. of six case-control studies, for example, concluded that the overall OR of 1.36 (95 % CI 1.12–1.65) was precluded by data heterogeneity, confounding factors and bias [85]. However, the most recently available meta-analysis, which included 23 randomized controlled trials, as well as 5 case-control and 3 cohort studies, concluded that acid suppression does indeed result in greater overall risk of acquiring pneumonia [86].

Clinical studies evaluating the risk for respiratory infections with acid suppression in

mechanically ventilated patients are lacking. A review of the subject by Vakil noted the paucity of data and concluded that available studies are outdated in the era of intravenous PPI, which raise gastric pH but also decrease gastric volume substantially [87]. Despite hard data either way, it appears that limiting acid-suppressive therapy to patients who are at serious risk for gastric ulcers has been emphasized in recent guidelines [88]. And extra caution is prudent in patients who are immunocompromised and have asthma or chronic obstructive lung disease, as these populations may be most vulnerable to acid suppression.

In summary, acid suppression results in bacterial overgrowth in the stomach and proximal small intestine. The clinical consequences of acid suppression and bacterial overgrowth are both nutritional and infectious. Bile acid deconjugation and decreased micronutrient dissolution in gastric juice may result in the malabsorption of vital nutrients, such as calcium and iron. Infectious consequences are both enteric and non-enteric, with a clear association with acid suppression and gastric pH. Clinicians must be cautious in prescribing long-term acid suppression, especially in vulnerable patient populations, such as hospitalized, ventilated, or immunocompromised patients, those with asthma or chronic lung disease, travelers, children, and the elderly. Clinical practice may extrapolate from studies that show that the risk of infections is directly related to the amount of time gastric pH is >4 and administer acid blockers in pulses, allowing for intermittent return of gastric acidity. Future studies should consider new generation, intravenous acid blockers that result in decreased gastric volume.

Conclusion

The microbiome is the sum collection of all microbes living within our individual body and an essential component of our being. It defines life as a continuum of biology that requires mutualism among organisms. It follows that many modern diseases are consequent not only to the breakdown of host biology, but also to a host response to alterations in the microbiome. In the upper gastrointestinal tract, the esophagus inhabits large numbers of firmicutes, mostly streptococcus, and a shift to bacteroidetes and nitrosamine-producing proteobacterial anaerobes appears to contribute to the disease process of reflux esophagitis and Barrett esophagus. Chagas disease megaesophagus is notable for a shift in the microbiota with increased prevalence of veillonella (Gram-negative, anaerobic clostridium). Although no data are available on the esophageal microbiota in cases of esophageal atresia, the common occurrence of respiratory disease in this patient population cannot be ignored, and future research may support a dysbiotic microecology that predisposes to respiratory disease. *H*. pylori, a major associative agent in gastric cancer, appears to dominate gastric ecology whenever present, favoring the growth of proteobacteria in expense of firmicutes and bacteroidetes. In general, acid suppression therapy results in increased bacterial counts in the stomach, leading to increased concentration of potentially dangerous strains, the deconjugation of bile acids, and an environment that is prone to nutrient malabsorption. Moreover, acid suppression appears to be associated with increased rates of both enteric and non-enteric infections, with a substantial risk for respiratory infections in vulnerable populations. Thus, the microbiome of the upper GI tract is a vibrant and important microecology with numerous functions, and its perturbance carries a risk for disease, from infections to inflammation and cancer.

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Part XXIII

Functional Gastropathology

Duodeno-Gastric Reflux and Duodeno-Gastro-Oesophageal Reflux

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Rok Orel

Introduction

Reflux of duodenal juice, containing bile and pancreatic secretions into the stomach, is called duodeno-gastric reflux (DGR). When contents of duodenal juice are mixed with contents of the stomach and reflux in the oesophagus, we are speaking of duodeno-gastro-oesophageal reflux (DGER). As bile is most commonly used for the detection of both DGR and DGER for research and clinical practice, the term "bile reflux", although being to some extent erroneous since it neglects other refluxate components, is often used synonymously for DGR and DGER.

Only a few studies have been published about DGR and DGER in children, and to the best of my knowledge, no such studies were done in infants. Therefore, a majority of data about physiology, pathology and clinical importance of DGR and DGER in this chapter derive from the results of studies made in experimental animal models and in adult patients. Moreover, a lot of knowledge about the importance of these refluxes came from studies performed in patients with partial or total gastrectomy who represent an in vivo model with excessive reflux of duodenal juice because of disrupted pyloric anti-reflux barrier. With total gastrectomy, no acid and pepsin secretions interfere with harmful effects of duodenal juice components and represent an ideal possibility for studying duodeno-oesophageal reflux.

Duodeno-gastric reflux is a physiological phenomenon. In healthy people, it occurs sporadically during phase II and III of the interdigestive migrating motor complexes (MMC) of the antrum and is regularly present postprandially [1] and during the night [2]. Beside the motility of stomach, pylorus and duodenum, the amount and concentration of bile, pancreatic and duodenal secretions as well as food intake and its composition are likely to determine the duration and quantity of DGR. Postprandial DGR is provoked by a great amount of bile and pancreatic secretions in the duodenum after a meal and enhanced duodenal motor activity. Lipid-rich meals are probably associated with higher reflux rates and a higher concentration and total amount of duodenal juice in the stomach when compared to protein-rich meals [3]. At the end of the antral phase III, reflux of bicarbonate and immunoglobulins IgA, but not bile, from the duodenum aided by duodenal retro-peristalsis may play an important physiological role in the chemical and immunological restitution of the gastric mucosal barrier function after the exposure to high acid and pepsin concentrations [4]. In this physiologic

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DGR, bile reflux is prevented by deviation to the gallbladder, probably by a phase III-associated occlusion of the sphincter of Oddi [5]. In view of the presumed role of MMC phase III as a gastrointestinal housekeeper, a role of gastric phase III in clearing of duodenal contents from the stomach seems likely [1].

The extent and duration of physiologic DGR in healthy persons show great interpersonal and intrapersonal day-to-day variability. The results of DGR detection are mostly dependent on the methods that were used. Even measurements with bilirubin monitoring system Bilitec 2000, probably the most accurate method for the DGR detection, which is explained in details in the section about the methods for DGR and DGER measurement, show very wide normal ranges. The median duration of bile presence in the stomach, the most frequently used marker for DGR, varied from 1.4 to 24.0 % of the day in healthy adults with an upper normal quartile cut-off levels from 7.8 to 72.0 % [6–12]. A comparison of gastric bilirubin exposure between proximal and distal sites within the stomach shows very big similarity that indicates that the duodenal refluxate is well mixed and evenly distributed within the stomach rather than concentrated more in the antrum and prepyloric area [9]. Since duodenal refluxate is relatively frequently present in the stomach, it is obvious that during gastro-oesophageal reflux episodes, it can reflux into the oesophagus.

Therefore, DGER can also be regarded as a part of normal physiology, although it does not appear regularly in all healthy people. Reflux episodes in healthy people are most common postprandially, and in healthy volunteers, more DGER was found during daytime than during the night. The median percentage of time with bile in the oesophagus in studies in healthy adults varied from practically none to up to 19.6 % [6, 13–16]. The amount of DGER may increase with ageing as more DGER was found in older volunteers [6]. For that reason, the adult normal values should not be directly extrapolated to children. Although the amount of DGER in healthy children has not been evaluated because of ethical reasons, the percentages of total time, upright time and supine time with bile in the oesophagus measured in children with gastro-oesophageal reflux symptoms but without reflux oesophagitis are comparable to those measured in healthy young adults (Table 128.1) [17]. After a reflux episode, refluxed material is cleared from the oesophagus by peristalsis and by washing with saliva end oesophageal gland secretions. Using simultaneous measurement of volume reflux by intraluminal impedance technique, acid reflux by pH monitoring and bile reflux by bilirubin absorptiometry with Bilitec 2000, we found out that volume bolus is cleared fast, followed by slower normalisation of oesophageal pH, whilst bile clears from the oesophagus as the last (unpublished observation). That can be explained by the fact that bolus clearance depends mostly on peristalsis, but the clearance of small amounts of refluxed material is the result of washing by saliva. Whilst acid can be chemically neutralised by relatively alkaline salivary and oesophageal glands' secretions faster than the washing process are finished, acid reflux episodes seem to finish faster than bile reflux episodes.

Table 128.1 Results of DGER measurement by Bilitec 2000 in children without oesophagitis

Bilirubin absorbance ≥0.14	Mean (SD)	95th percentile
% total time	0.3 (0.93)	1.17
% upright time	0.45 (1.44)	1.77
% supine time	0.13 (0.8)	0.5

Methods for Detection and Measurement of DGR and DGER

Several methods have been used in the past for the detection of DGR and DGER; however, each of them has its own strengths and shortcomings.

The observation of bile in the stomach or oesophagus during endoscopy is a poor indicator because of the intermittent nature of DGR and DGER and its clinical significance has never been demonstrated. Therefore, the endoscopy has a low accuracy and a low predictive value, and even histological picture of the mucosa, although suggestive of bile reflux, is not pathognomonic [18].

Aspiration studies with chemical analysis of aspirate contents produced a lot of scientifically important information but are inappropriate for everyday medical practice. Whilst using single aspiration yields a high rate of false-positive and false-negative results, frequent or even continuous sampling overcomes this drawback but may induce refluxes by creating pressure gradient [19].

Detection of bile acids, bilirubin or other constituents of duodenal juice in mouth saliva has been applied as a marker for DGER [20], but this method has not been validated enough and its accuracy is very questionable.

Scintigraphy is another possible method to detect DGR and DGER. A radioactive marker, for example, iminodiacetic acid (HIDA), which is rapidly eliminated through the liver and the bile ducts into the duodenum, is given to patients. Intermittent imaging of abdomen with gamma camera reveals refluxes as the appearance of the marker in the gastric or oesophageal area. Although non-invasive, it is relatively insensitive, because of the overlap of other organs and patient movement and especially due to the intermittent nature of refluxes, particularly the oesophageal one [21].

Detection of DGR and DGER by pH monitoring is based on the assumption that these refluxes cause an increase of pH over 7 because of alkaline nature of the duodenal juice. A term "alkaline reflux" was used as a synonym for DGR and DGER [22]. Simultaneous pH monitoring in oesophagus and stomach was frequently used in an effort to relate alkaline shifts in the stomach to those in the oesophagus [21]. However, detection of DGR and DGER with more objective methods revealed that these refluxes infrequently cause an increase in pH over 7. Moreover, the majority of bile reflux episodes take place at acidic or neutral pH [23–25]. Therefore, a pH of less than 7 does not exclude DGR and DGER. A pH above 7 may be caused by other factors, such as saliva, food, bicarbonate secreted by oesophageal submucosal glands, etc. [21]. DGR and DGER can therefore not be detected by pH monitoring alone, and the term "alkaline reflux" is a misnomer for describing refluxes of duodenal juice into the stomach and the oesophagus.

A fiberoptic spectrophotometer, Bilitec 2000, detects DGR and DGER independently of pH and can be used in an ambulatory setting [26]. This system utilises the optical property of bilirubin, the main biliary pigment, that has a characteristic spectrophotometric absorption band with a peak between 390 and 460 nm. The basic working principle of the instrument is that absorption of light near these wavelengths implies the presence of bilirubin and, therefore, represents bile reflux. In vitro validation experiments using Bilitec in differing dilutions of a bilirubin solution revealed a linear correlation between absorbance and bilirubin concentration, but in acidic environment ($pH < 3.5$), the bilirubin concentration can be underestimated by at least 30 % [27, 28]. It has been shown that bilirubin absorbance also correlates with the concentration of bile acids; however, this relationship was weaker in vivo [29]. In clinical practice, the method is not used for measuring bilirubin concentrations but to detect the presence or absence of bile in the stomach or in the oesophagus. For that purpose, threshold values of absorbance have been set on experimental basis to be sensitive and specific enough for bile detection. Absorbance ≥ 0.14 is usually applied for DGER detection, but different threshold values, ranging from ≥ 0.14 to ≥ 0.30, are used for DGR [6, 30]. By increasing the threshold value, the specificity of the method increases, but its sensibility decreases. The results are expressed as percentage of time of the recording with the presence of DGR or DGER. Ingested substances, in particular heavily coloured foods, may absorb light at the same wavelengths as bilirubin, thus interfering with the accuracy of the method and generating false-positive measurements. For that reason, a special "white diet" is recommended during monitoring [14, 31, 32]. Another drawback of the method is a possibility that a particle of food or other substance obstructs the tiny gap between fiberoptic probe and reflecting cap at its end (Fig. 128.1) and causes the disappearance of the signal [26]. Despite its limitations, bilirubin spectrophotometry represents the most practical and accurate method for DGR and DGER detection for both experimental and clinical purposes.

Fig. 128.1 The tip of a fiberoptic spectrophotometer Bilitec 2000

Multichannel intraluminal impedance is a method that enables detection of volume reflux independently of its pH. Usually, it is used simultaneously with pH monitoring so reflux episodes can be recognised as acid, weakly acid and alkaline [33]. However, impedance cannot detect a chemical composition of the refluxed material and is therefore inappropriate for the detection DGR and DGER.

In the future, new technologies using biosensors specific for bile acids or other reflux constituents seem a promising practical tool for DGR and DGER measurement. Such a biosensor could be devised using molecular imprinting technology (MIP) based on recognition characteristics of polymers that have complimentary size, shape and binding site to specific substrates and have already been applied to recognise steroids such as cholesterol and bile acids which share the same four-ring structure as other steroids [34].

Mechanisms of Inflammation and Oncogenesis Produced by the Duodenal Refluxate Constituents

Numerous studies using animal models or tissue culture experimental models revealed that duodenal juice constituents play an important role in the development of inflammation and oncogenesis in the stomach and the oesophagus.

Trypsin and perhaps other pancreatic proteases cause tissue damage and release of intracellular inflammation mediators [35]. Trypsin is thought to digest intercellular substances and surface structures that contribute to the maintenance of cohesion between cells, causing the dilution of intercellular spaces and the shedding of epithelial cells [36–38]. It has been shown that trypsin induces the expression of pro-inflammatory cytokines on epithelial cells through the activation of specific receptors, protease-activated receptors (PARs). Human oesophageal cells stimulated with trypsin produce interleukin-8 and prostaglandin E_2 [39]. Trypsin's activity depends on pH and is optimal in the pH range from 5 to 8.

Another important component of duodenal juice is lysolecithin that is formed when pancreatic phospholipase A hydrolyses the lecithin in bile. Studies have demonstrated that in the presence of acid, lysolecithin is able to injure oesophageal mucosa, causing almost complete tissue breakdown [36, 40].

Bile salts are normal duodenal juice components. Human liver converts an average of 0.78–1.29 mmol (300–500 mg) of cholesterol into bile acids daily. These primary bile acids, cholate and chenodeoxycholate, are synthesised by hepatocytes in a ratio of 2–1. Secondary bile acids, deoxycholic acid and lithocholic acid, are formed from primary bile acids as metabolic by-products of intestinal bacteria, most importantly *bacteroides* and *bifidobacteria*, by deconjugation and 7α-dehydroxylation. Prior to secretion into bile, 98% of bile acids are conjugated with taurine or glycine in a ratio of about 3–1. Bile acid synthesis is regulated by feedback inhibition from reabsorbed bile acids from the gut reaching the liver via the portal vein. Bile acids have to be deconjugated by intestinal bacteria before absorption and are reconjugated in the liver before re-entering the bile. This enterohepatic circulation maintains a composition of human bile consisting of 54% cholic, 31% chenodeoxycholic, and 15% deoxycholic acid, of which about 80% is conjugated with taurine and 20% with glycine [41]. Damaging effect of bile salts on the mucosa is dependent on their conjugation state. The conjugation state depends mostly on the pH. When the pH is equal to the pKa, the bile acid is half ionised and half protonated, the ionised half being soluble [40].

Although the mechanism by which bile acids damage the mucosa is not fully understood, available studies suggest more hypotheses. The first is that bile acids damage mucosal cells by their detergent property and solubilisation of their lipid membranes [38]. This theory is supported by studies in gastric mucosa in which bile acid mucosal injury was correlated with the release of phospholipids and cholesterol into the lumen [42]. The second hypothesis suggests that bile acids gain entrance across the mucosa because of their lipophilic state, causing intramucosal damage by disorganising membrane structure and interfering with cellular metabolism [38]. Once bile acids have penetrated the mucosal barrier, they are trapped inside the cells by intracellular ionisation that results in severalfold increase in their intracellular concentration [43, 44]. The unionised lipophilic forms predominate at more acidic pH for conjugated bile acids (i.e. pKa 1.9) and at more neutral pH for unconjugated bile acids (i.e. pKa 5.1) [38]. As the damage caused by bile salts depends on their solubility, conjugated bile salts cause mucosal damage under acidic and unconjugated under neutral and alkaline conditions [36, 37]. Moreover, by dissolution of cell membranes and tight junctions, bile acids open the doors to other harmful substances such as acid, pepsin and pancreatic enzymes [45].

It is known that bile acids can also stimulate cell proliferation and promote tumorigenesis and are therefore implicated in the development of Barrett's oesophagus, gastric and oesophageal squamous cell carcinoma and adenocarcinoma [35, 46–50]. Damaged mucosal cells produce inflammatory mediators such as cytokines, which recruit inflammatory cells to the site of inflammation. These cells produce free radicals whose primary role is to remove the damaged cells, but they may also induce genetic mutations. Bile acids are known to induce oxidative stress and DNA damage [51, 52]. They can induce up-regulation of superoxide-generating NADPH oxidase NOX5-S expression and increase in cell proliferation depend on activation of TGR5 receptor (a bile acid receptor) and Cαq protein which is involved in hydrogen peroxide production [53]. Whilst most of these changes will lead to cell death, others may confer a survival advantage and lead to a clonal expansion of the premalignant, Barrett's or malignant cell type [54].

One of the characteristics of premalignant and especially malignant cells is also their loss of differentiation. The vitamin A derivate retinoic acid is an inducer of differentiation, and there is evidence that bile acids compete for one of its nuclear receptors [55]. Cyclooxygenase (COX) is the enzyme responsible for the rate-limiting step in the production of prostaglandins. Whilst COX-1 is constitutively expressed in the normal gastric and oesophageal mucosa and has a protective function, the role of COX-2 includes inflammation, cell adhesion, blocking apoptosis, invasion, angiogenesis and metastasis and is induced by inflammatory and cancerous processes [54]. Bile acids have been shown to stimulate production of COX-2 and prostaglandins such as prostaglandin E_2 which may play an important role in cell metaplasia, dysplasia and tumorigenesis [56, 57]. They can also activate mitogen-activated protein (MAP) kinase and NF-κB pathways, thereby increasing cell proliferation and decreasing cell apoptosis [53].

Experimental studies suggest that bile acids can directly induce DNA changes which may lead to mutations and may be thus implicated in the initiation of carcinogenesis [58]. Many chromosomal losses and gains were detected by a high-resolution oligonucleotide comparative genomic hybridisation in the neoplastic cells developed by experimental reflux of duodenal juice [59]. Moreover, by entering cellular nucleus and binding to nuclear receptors, bile acids may induce the expression of oncogenes. For example, the proto-oncogene C-myc is up-regulated and expression is increased by exposure to bile acids [60].

In conclusion, duodenal juice contents as pancreatic enzymes, lysolecithin and conjugated and unconjugated bile acids are implicated in mucosal damage, inflammation, metaplasia and malignant alteration through different mechanisms; however, their detrimental effect depends on pH. In acidic conditions, conjugated bile acids and lysolecithin can damage mucosa in synergism with hydrochloric acid and pepsin from the

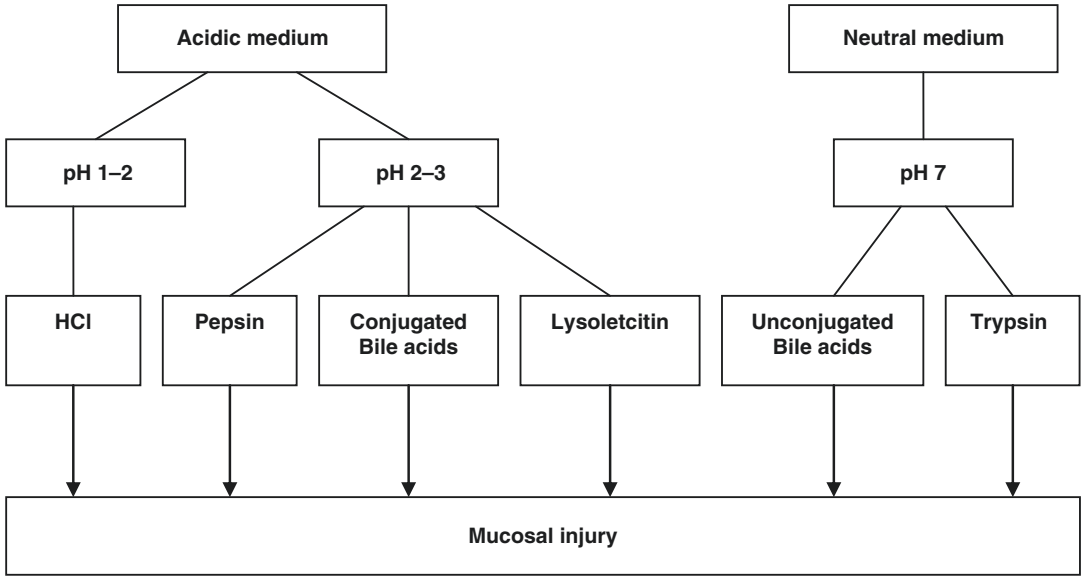

Fig. 128.2 A schematic representation of pH dependence of different agents responsible for mucosal injury

gastric juice. At neutral or alkaline pH, unconjugated bile acids and pancreatic trypsin can damage gastric and oesophageal mucosa (Fig. 128.2).

Clinical Presentation

Excessive DGR and DGER have been suggested to be involved in the pathogenesis of several foregut diseases such as chemical gastritis, functional dyspepsia, reflux oesophagitis, Barrett's oesophagus and gastric and oesophageal carcinoma. Symptoms are non-specific such as upper abdominal pain or discomfort, postprandial fullness, regurgitation and, occasionally, bile vomiting. Therefore, the objective diagnostic methods are necessary to prove pathologic amount of reflux as well as its connection with the disease.

A lot of knowledge about the importance of DGR and DGER has arrived from observations in surgical patients. In patients after partial or total gastrectomy with gastroduodenostomy (Billroth I), gastrojejunostomy (Billroth II) or reconstruction with biliary diversion (Roux-en-Y), excessive DGR had been documented by objective measurements with intragastric bilirubin spectrophotometry, caused by the loss of pyloric sphincter functioning as a physiologic barrier to retrograde flow of duodenal contents into the stomach [10, 61, 62]. Not only dyspeptic symptoms but also remnant gastritis, gastric ulcerations, gastric stump carcinoma, gastro-oesophageal reflux disease and oesophageal adenocarcinoma have been attributed to excessive DGR in these patients [10].

Moreover, excessive DGR with its consequences has also been discovered in patients who underwent cholecystectomy, endoscopic sphincterotomy or other hepatobiliary operative procedures [63–65]. In contrast with healthy subjects in whom DGR was present most often postprandially, in cholecystomised patients, bile is present in stomach also during fasting [65]. This profile may be explained by the surgical loss of the normal gallbladder reservoir for bile, which is then excreted into the duodenum at the same rate it is secreted by the liver. Thus, after cholecystectomy, more bile enters the duodenum when fasting and less after eating compared with subjects with a normal gallbladder. The more constant presence of bile in the duodenum creates conditions predisposing to increased duodeno-gastric bile reflux. Moreover, a number of motility abnormalities were noted after cholecystectomy [66]. Phase II in the antrum, the "clearance" wave, was found to occur at a significantly slower

rate. Also, there was less build-up to phase III of the interdigestive migrating motor complex, with a lengthened phase I and reciprocally shortened phase II. Furthermore, the phase III front migrates down the duodenum at half the speed that it does in healthy subjects. This may slow clearance of the increased proximal duodenal pool of biliary secretions, which is then available to reflux into the stomach where it is ineffectively cleared [66]. In children operated for choledochal cyst, excessive DGR was found following hepaticoduodenostomy but not following Roux-en-Y hepaticojejunostomy [67].

In contrast to this, serious gastric pathology caused by primary excessive DGR without previous gastrointestinal surgery is relatively rare. It has been postulated that DGR produces consistent histological changes in the gastric mucosa, so-called chemical or reactive gastropathy or bile reflux gastritis. The histological feature most strongly associated with DGR was intestinal metaplasia at the gastric antrum. DGR was also positively associated with the severity of glandular atrophy, chronic inflammation, lamina propria oedema and foveolar hyperplasia. As a result, a histological index, the bile reflux index (BRI), was derived. Evaluation studies showed that its values above a threshold 14 have a sensitivity of 70 % and a specificity of 85 % for a bile acid concentrations >1.00 mmol/l, which is the upper limit of physiological reflux [68]. Increased DGR has been incriminated in the genesis of symptoms in patients with functional dyspepsia. Although in some studies significantly increased DGR has been found in these patients compared to controls [10], other groups found the role of DGR to be minor since its amount during fasting was normal and only slightly increased after eating [65]. In patients with dyspeptic symptoms with pathologic amount of DGR, the mucosal lesions such as active inflammation, chronic inflammation, intestinal metaplasia, atrophy and *Helicobacter pylori* infection in the whole stomach were more severe than those in dyspepsia patients without DGR, and the bile reflux time was well correlated with the severity of pathological changes [69]. However, the relationship between *H. pylori* infection and DGR remains controversial. Some data suggest that *H. pylori* may induce DGR, and therefore both may act synergistically on the gastric mucosa, causing chronic gastritis, which may lead to the carcinoma sequence [68, 70, 71]. On the other hand, there are reports proposing that DGR decreases *H. pylori* colonisation and even suggesting to use bile acids for the treatment of *H. pylori*-related gastritis [72, 73]. However, by comparing the amount of DGR before and after *H. pylori* eradication [74], and the presence of *H. pylori* infection in patients with and without DGR [75], no causative relationship could be proved between DGR and *H. pylori* infection. Primary DGR has been rarely reported as a proposed mechanism of gastric pathology in children unresponsive to classical antacid therapy [76].

The principal role of acid reflux of gastric juice in the development of reflux oesophagitis, Barrett's oesophagus and oesophageal cancer has been well established. First ideas about the importance of DGER came from the observations in patients with atrophic gastritis, pernicious anaemia and following gastrectomy who developed oesophagitis despite practically absent gastric acid secretion [77–79]. Although DGER can be a consequence of excessive DGR, it can appear from either increased or normal gastric exposure to duodenal contents [80]. Therefore, pathologic DGR can be an important mechanism but is not a prerequisite for increased DGER. In contrast with paucity of convincing clinical evidence that DGR can produce serious pathology in intact (non-operated) stomach, numerous quality clinical studies elucidated the importance of DGER in oesophageal pathology, both in adults and children.

Some but not all of the studies using gastric or oesophageal aspiration and chemical analysis of the aspirate showed an increase in the presence of bile acids in gastro-oesophageal reflux (GERD) patients in comparison with healthy controls [45]. The differences in the results can be partially explained by different techniques of sampling and particularly by different methods of chemical analysis. In addition, particularly increased bile acid concentration was found amongst patients with Barrett's oesophagus, with

the highest concentrations amongst those with complicated Barrett's oesophagus (stricture, ulcer, dysplasia) [81, 82]. However, even in studies which found increased amounts of bile acids in GERD patients, their concentration seldom exceeded 1.0 mmol/l, the concentration regarded high enough to produce oesophageal mucosal lesions [83].

Although it is clear today that increase of pH above 7 cannot be regarded as a marker of DGER, oesophageal pH monitoring was used in the past to trace for "alkaline reflux". Several groups published their findings of significantly higher amounts of both acid and alkaline reflux in patients with complicated oesophagitis, Barrett's oesophagus and complicated Barrett's oesophagus [84]. These investigators went on to suggest that prolonged exposure of oesophageal mucosa to duodenal contents alone may promote the development of complicated Barrett's oesophagus and even adenocarcinoma.

Most of the knowledge about the clinical importance of DGER in oesophageal pathology arrives from studies using simultaneous oesophageal pH monitoring and bilirubin spectrophotometry with Bilitec 2000. These studies again pointed out the importance of DGER in the development of Barrett's oesophagus as in the majority of them patients with Barrett's oesophagus had a significantly greater exposure to both acid and duodenal contents than patients with reflux oesophagitis or healthy controls [14, 85, 86]. Moreover, it seems that patients with long segment and complicated Barrett's oesophagus have particularly increased exposure to DGER [82, 87]. In comparison with patients with short segment Barrett's oesophagus, they have similar acid reflux but significantly greater reflux of duodenal contents. With some exceptions that did not find significant differences in GERD between controls and patients with reflux oesophagitis [14], a gradual increase of both acid reflux and DGER has been proven across the GERD spectrum, being the lowest in healthy persons and in patients without oesophagitis, higher in patients with reflux oesophagitis and the highest in patients with Barrett's oesophagus [15, 86, 88]. Barrett's oesophagus is a rare disorder in children; therefore, paediatric studies did not include patients with Barrett's oesophagus. However, both acid reflux and DGER exposure were found to increase stepwise with the severity of oesophagitis. They were lower in children with GERD symptoms but without reflux oesophagitis compared with children with reflux oesophagitis, and children with severe oesophagitis (Los Angeles grades C and D) had more refluxes than those with mild oesophagitis (Los Angeles grades A and B) (Fig. 128.3) [17].

Duodeno-gastro-oesophageal reflux may cause symptoms, although symptom episodes in patients with GERD seem to be more often related to acid reflux episodes [89, 90]. There is a growing evidence that pathologic amounts of DGER without pathologic acid reflux can result in erosive reflux oesophagitis both in adults [91–94] and children [17, 95]. In my experience, a majority of children without oesophagitis has no pathologic refluxes. Isolated pathologic acid reflux or isolated DGER cause mild oesophagitis, and a combination of both cause severe oesophagitis (Fig. 128.4) [17]. However, in some patients with reflux oesophagitis or even Barrett's oesophagus, the results of both pH monitoring and bilirubin spectrophotometry can be normal [96].

Duodeno-gastro-oesophageal reflux may play an important role in the pathophysiology of proton pump inhibitor-refractory GERD [97, 98]. Although pathologic acid reflux, pathologic DGER or a combination of both were found in adults and children not responsive to the therapy with proton pump inhibitors (PPIs), acid exposure did not differ according to the presence of oesophagitis, but patients with substantial oesophagitis had significantly higher DGER exposure than those without oesophagitis [98, 99]. DGER may also participate in the development of more severe forms of GERD in children with additional risk factors like neurological and developmental disorders, cystic fibrosis and operated anomalies of upper gastrointestinal tract. Significantly higher gastric bilirubin levels were found in children with cystic fibrosis when compared with healthy subjects that may result in exaggerated DGER [100].

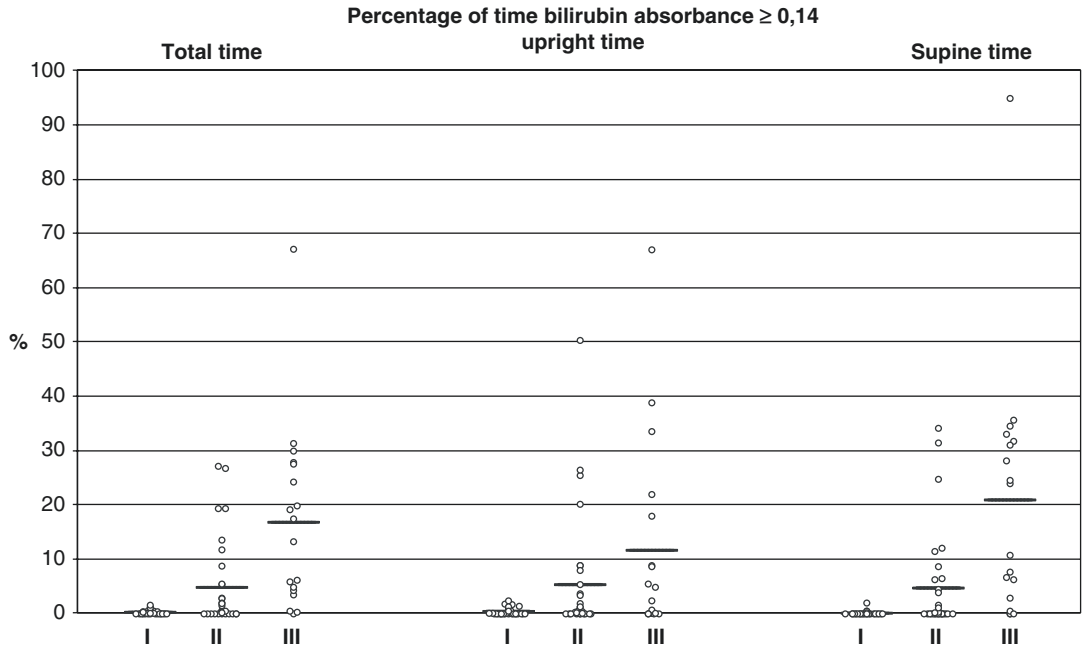

Fig. 128.3 Results of 24 h DGER monitoring with fiber-optic spectrophotometer expressed as mean and individual values in children without oesophagitis (I), with mild to moderate oesophagitis (II) and with severe oesophagitis (III) for percentages of total time, upright time and supine time with bilirubin absorbance ≥0.14 [17]

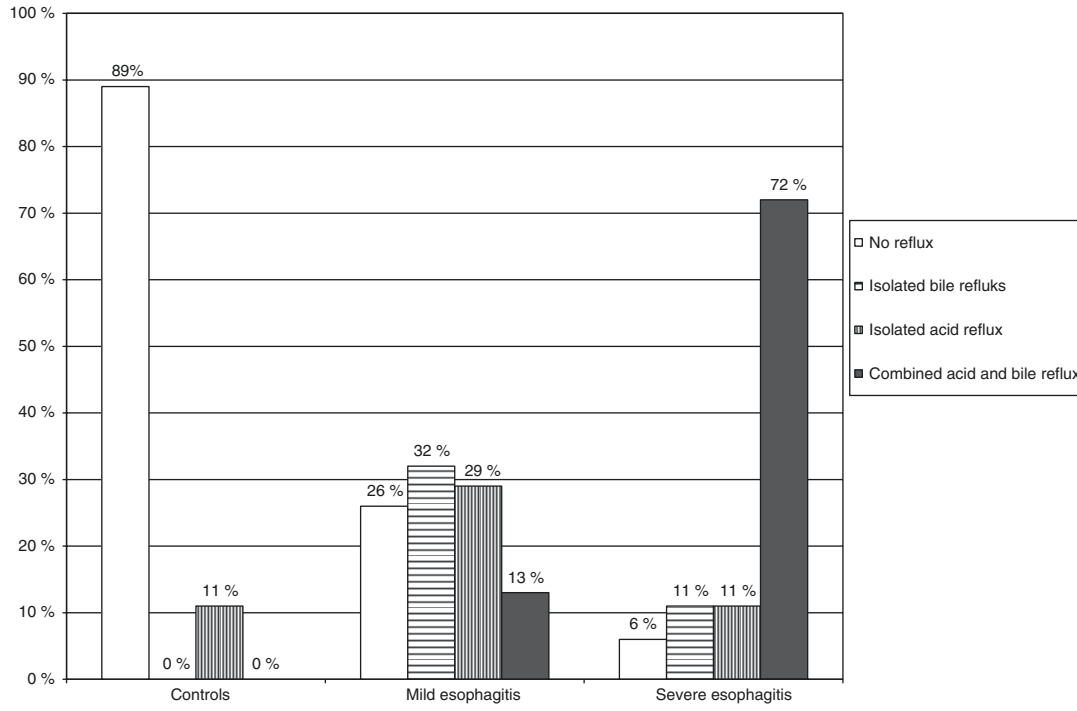

Fig. 128.4 Percentage of patients with no pathologic reflux and with three different patterns of pathologic reflux (isolated bile reflux, isolated acid reflux and combined acid and bile reflux) in the groups of children without oesophagitis, with mild to moderate oesophagitis and with severe oesophagitis [17]

As DGER or its effects may extend beyond the oesophagus, it may cause or contribute to a variety of supra-oesophageal manifestations. Pathological DGER was found in patients with unexplained excessive throat phlegm [101]. Significant higher prevalence of symptoms and findings of laryngeal damage including laryngeal neoplastic lesions was reported in patients after gastric surgery with presence of bilirubin and bile acids, indirect markers of DGER, in saliva [20]. Moreover, pathological acid reflux and especially excessive "alkaline" reflux were found to be elevated and could be implicated into the pathogenesis of neoplastic lesions of the pharynx and larynx [102].

Simultaneous oesophageal pH monitoring and bilirubin spectrophotometry explained the exact relationship between DGER and oesophageal pH. Firstly, these studies revealed that DGER rarely coincide with so-called alkaline shift (a rise of pH over 7), suggesting that the term "alkaline reflux", previously often used synonymously with DGER, is a misnomer [24, 88]. Secondly, DGER appears across the whole oesophageal pH spectrum. Whilst some studies found DGER episodes most frequently between oesophageal pH 4 and 7 [14, 24], the others discovered the majority in an acidic environment (pH < 4) [15]. It was shown that in children, DGER episodes most frequently begin at pH between 6 and 7, the pH of an empty oesophagus. However, after the beginning of an episode, oesophageal pH may change. The pH of the refluxate depends on the proportions of acid gastric juice, food and duodenal juice in it. It is interesting that in children without oesophagitis, relative duration of DGER was longest between pH 5 and 6, in children with mild oesophagitis between pH 4 and 5, whilst in those with severe esophagitis, it was between pH 2 and 4 [25]. From these observations, one can hypothesise that the lower the pH at which DGER occurs, the more severe the oesophageal damage, resulting from simultaneous effects of gastric and duodenal juice components.

Therapy

Both pharmacological and surgical therapies of excessive DGR and DGER have been profoundly studied.

Specific aims of treating DGR and DGER with medications can be directed at three components: decreasing gastric acid secretion, promoting motility and gastric emptying and neutralising or binding bile acids and making them less injurious to the gastric and oesophageal mucosa [103].

Acid suppression, particularly with PPIs, is the mainstay of treatment of gastric and oesophageal diseases. Several clinical studies revealed that treatment with PPIs and even H_2-blockers dramatically decreases not only acid reflux but also reflux of duodenal juice into the oesophagus, both in adults [88, 104–107] and children [108] (Fig. 128.5). The proposed mechanism is reduction of the volume of gastric secretions, with less fluid available in the stomach for any DGR to mix with and thence to reflux into the oesophagus. This mechanism may also explain the reduction in DGR to the upper part of the stomach, a prerequisite for DGER [104]. Moreover, some studies showed that acid suppression therapy can influence gastric and duodenal motility by increasing antral phase III MMC, which have the role of "street sweeper" and clean the duodenal reflux contents from stomach. MMC III is evoked by a presence of bile and pancreatic juice and neutralisation of acid in the duodenum but can be inhibited by acidic pH. Therefore, PPIs may also decrease DGR and DGER through increasing MMC III due to increased duodenal pH [107]. The second proposed mechanism seems more likely since studies using combined oesophageal pH monitoring and intraluminal impedance revealed that therapy with PPIs does not affect volume reflux into the oesophagus [109]. It should not be forgotten that several DGER components such as conjugated bile acids and lysolecithin are most dangerous to the oesophageal mucosa at acidic pH when their harmful effect is synergistic with gastric acid and pepsin. Their activity can be neutralised by rising oesophageal refluxate pH with acid suppression therapy.

Cisapride promotes the release of acetylcholine from the myenteric plexus and thereby improves gastric emptying and increases lower oesophageal sphincter pressure. Several studies showed that cisapride relieves symptoms in both adult [110] and paediatric [98, 111] patients with excessive duodenal reflux. However, the results of studies using objective

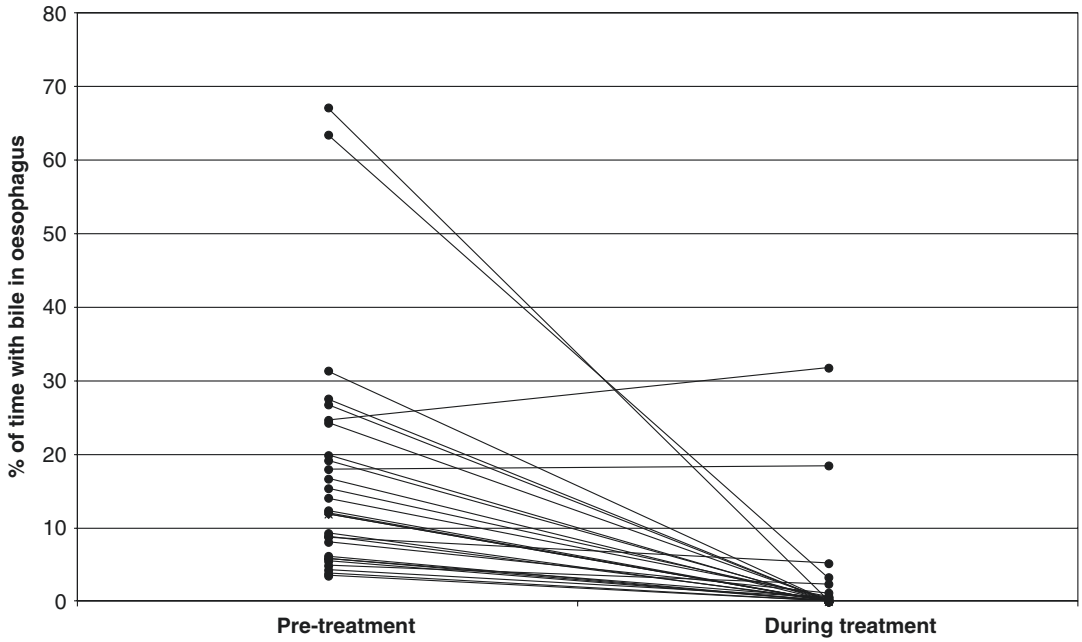

Fig. 128.5 The effect of therapy with omeprazole on duodeno-gastro-oesophageal reflux in children [108]

measurements of DGR or DGER for assessment of the efficacy of cisapride are conflicting. Significant decrease of DGER was observed during therapy with cisapride in a placebo-controlled trial in postgastrectomy patients [110], but not in patients with gallstones and intact stomach [112]. Cisapride is not available any more, as it has been withdrawn from the market because of its interactions with many other drugs and serious side effects.

Domperidone, a peripheral dopamine (D_2) receptor antagonist, acts as an antiemetic and prokinetic agent through its effects on the chemoreceptor trigger zone and motor function of the stomach and small intestine, thus promoting gastric emptying by augmenting gastric peristalsis and improving antroduodenal coordination. Domperidone was effective both in amelioration of symptoms and in decreasing nocturnal bile reflux into the stomach in patients with functional dyspepsia [113].

Erythromycin, an antibiotic with prokinetic properties, almost completely normalised DGR in all patients with pathological DGR after biliary surgery [114].

Baclofen, the gamma-aminobutyric $acid_B$ ($GABA_B$) agonist, inhibits the occurrence of transient lower oesophageal sphincter relaxations that are the main pathophysiological mechanism underlying the gastro-oesophageal reflux. In a study in patients with DGER refractory to PPIs, baclofen reduced both the number and the duration of DGER episodes significantly [115].

Cholestyramine is a basic anionic exchange resin that binds bile salts. In an uncontrolled study, cholestyramine helped some patients with mild bile reflux gastritis [116], but this finding was not confirmed in a later randomised, double-blind study [117].

Aluminium hydroxide but not magnesium hydroxide antacids absorb conjugated bile acids and lysolecithin with an affinity and capacity comparable with cholestyramine. Their efficacy in symptom relief of bile reflux gastritis was equivalent to cholestyramine but not better than placebo [117].

Ursodeoxycholic acid (UDCA) is potentially effective by changing the composition of the refluxed bile, which may be less noxious to the gastric and oesophageal mucosa. In a placebo-controlled study in patients with bile reflux gastritis, a therapy with UDCA resulted in significant amelioration of symptoms but had no effect on the macroscopic and microscopic appearance of the gastric mucosa [118].

Sucralfate is the basic aluminium salt of sulphated sucrose that adheres to exposed proteins

in damaged mucosa, protecting them from acid, pepsin and bile acids. In a placebo-controlled study in patients with bile reflux gastritis, sucralfate lowered the gastric inflammatory cell scores but was not associated with improvement of symptoms [119].

Remnant chemical gastritis as a consequence of excessive DGR after subtotal gastrectomy can probably be prevented by choosing reconstructive procedures which decrease retrograde flow of duodenal juice and particularly bile into the stomach. Studies revealed that Roux-en-Y reconstruction is better than Billroth I or II [120, 121]. With Roux-en-Y operation, a 45–60 cm-long isoperistaltic limb of jejunum is created between partially resected stomach and jejunal limb draining the pancreatic biliary system [103]. The Roux-en-Y operation was shown to preserve the cardia and the position of the remnant stomach better than other procedures. In patients after resection of the extrahepatic bile duct, Roux-en-Y hepaticojejunostomy was more effective in prevention of excessive DGR than hepaticoduodenostomy [67]. The Roux-en-Y anastomosis is also a successful therapy for patients with intractable symptoms of remnant gastritis and documented increased DGR after other gastric operations [122, 123]. However, side effects include ulceration, delayed gastric emptying and dumping [103]. Duodenal switch is an operation in which the stomach and proximal 5–7 cm of the duodenum are left intact. The jejunum is divided about 25 cm distal to the ligament of Treitz. The distal limb is anastomosed end to end to the proximal portion of the duodenum, and the proximal limb of the jejunum is anastomosed end to side to the distal jejunum. This may be the preferred operation in patients with excessive DGR and intact stomach as complications are markedly reduced compared to Roux-en-Y operation [103, 124]. However, such aggressive surgery is nowadays not a realistic therapeutic option in patients and especially in children with pathology due to excessive DGR and DGER without previous gastric or biliary operation. Exceptions to this rule are patients with severe gastro-oesophageal reflux disease refractory to pharmacological therapy who may benefit from anti-reflux surgery. Several studies showed that DGER adequately decreases after Nissen fundoplication [125, 126].

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Gastric Pacing

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Introduction

Gastric pacing is used in the treatment of gastroparesis. Although fewer children are affected than adults, their symptoms are equally debilitating. Children often require hospital admission and parenteral feeding, and they suffer disruption to their schooling. The diagnosis, however, may not be as easy to make in children, either because it might be seen as part of another condition or because of its lack of recognition amongst practitioners [13].

Stimulation of the stomach has been considered a possible treatment for the symptoms of gastroparesis for approximately 50 years. Initially the generated stimulus mirrored the natural frequency of gastric motility in a hope to entrain the stomach, so-called gastric pacing. Animal studies produced a combination of stimulus frequency and energy that could produce the optimum motility, called gastric electrical stimulation (GES). The theory was applied to a young insulin-dependent diabetic woman with encouraging results. In 2000, an implantable unit became widely available which has gained US Federal Drug Administration (FDA) approval, but not UK National Institute for Health and Care Excellence (NICE) approval.

Gastroparesis

Gastroparesis is a disorder defined by objective evidence of delayed or disordered stomach emptying in the absence of mechanical obstruction.

The most common symptoms are severe nausea and vomiting, but others include early satiety, postprandial fullness, bloating, abdominal discomfort, epigastric pain and/or weight loss. In adults, the commonest causes are diabetes, idiopathic and surgery, in particular with vagotomy. In children, postviral illness is the usual cause and should be self-limiting, taking several months to resolve [11]. The next commonest causes in children are idiopathic, which tends to be longer lasting and more severe, and also following surgery. Rarely, it is due to an autoimmune illness, or as part of a paraneoplastic process. Diabetic gastroparesis can be recognised in children, as seen in three cases of insulin-dependent diabetic children aged between 10 and 15 years [23].

Diagnosis

Once neoplastic and obstructive causes have been excluded, gastroparesis can be confirmed

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using scintigraphy, ultrasonography, ^{13}C-breath testing, magnetic resonance imaging, swallowed-capsule telemetry, antroduodenal manometry and electrogastrography (EGG) [21]. Scintigraphy is considered the gold standard investigation, but is not always available. It should be performed with a calorie- and nutritional-standardised solid meal labelled with technetium-99m sulphur-colloid bound to egg, rather than a liquid meal, as liquids may have normal gastric emptying times. Measurements are taken at 2 h and 4 h post-ingestion, and can be expressed as percentage remaining within the stomach at these times. Ultrasonography can be very useful in children as it is less invasive and only requires the ingestion of a standardised meal, although the quantity ingested may vary according to age. It requires a skilled ultrasonographer to undertake measurements of various parameters of the stomach. Antroduodenal manometry can provide information on whether the delayed gastric emptying is due to antral or duodenal causes, and also whether a neurological or muscular disease may be causing it. EGG is a noninvasive technique and was introduced in 1921 by Alvarez. By placing electrodes cutaneously on the long axis of the stomach, it is able to measure the slow wave, generated by the stomach's pacemaker, the interstitial cells of Cajal. The slow wave is not directly associated with contractile activity, but with the spatial and temporal organisation of gastric contractions [16]. It has been found that 75 % of patients with gastroparesis have an abnormal EGG, and also experience more severe symptoms. A study from 2004 [17] investigated GES using EGG on 15 patients with gastroparesis. It was shown to enhance the slow-wave amplitude and propagation velocity and resulted in a significant improvement in nausea and vomiting but did not entrain the gastric slow wave or improve gastric emptying. There appears to be no difference in myoelectrical activity in children compared to adults from age, gender or body mass index (BMI), as measured in 55 children aged between 6 and 18 [16]. EGG has demonstrated antral hypomotility in diabetic children [6].

Treatment

Coincidental with treating the symptoms of gastroparesis, the electrolyte imbalances that it may produce must also be treated. Hyperglycaemia induces delayed gastric emptying and reduces the efficiency of prokinetics, so normoglycemia should be aimed for. Dietary changes aim for an easily digestible meal which can be emptied quickly using liquid [11] or soft, frequent, low-fat, low-fibre meals and high-calorie liquid supplements [4]. First-line pharmacotherapy treatments use prokinetic agents such as erythromycin, metoclopramide and domperidone and antiemetics including phenothiazines, antihistamines and 5-HT receptor agonists.

Local treatments for gastroparesis have employed the injection of Botox into the pylorus, as pylorospasm has been observed in diabetic gastroparesis, but a double-blind controlled crossover study found no improvement over placebo. Until the advent of gastric stimulation, via pacing, the next progressive step in the management of gastroparesis was surgery employing the palliative procedures of venting gastrostomy, and pyloroplasty for gastric emptying, and providing enteral nutrition with a feeding jejunostomy [14, 22]. When all other treatments fail, a subtotal gastrectomy, or as a last resort, total gastrectomy can be used, but these carry higher morbidity and mortality rates [10]. To date there has only been one report of a paediatric Billroth I procedure in a 15-year-old for intractable nausea who had undergone three attempts at repair of a congenital diaphragmatic hernia [15].

Gastric Electrical Stimulation

History

Gastric pacing was first documented as a treatment for ileus in 1963 [3]. The desire to create a series of contractions that mimicked the normal gastric pattern was based on the assumption that it was the prolonged gastric emptying that produced the debilitating symptoms of intractable

vomiting and nausea [20]. The technique began with the temporary placement of electrodes connected to an externally housed generator unit. The stimuli produced were of high energy and a frequency comparable to intrinsic contractions, namely, three per minute. In 1997 the first case of stimulation at a higher frequency was published. The background research for choosing this frequency was based upon a canine model which studied varying combinations of frequency and energy of the generated pulses [7]. They found the frequency which produced the largest motility index and entrained the stomach was four times the physiologic rate. These results were then applied to a human case by the same research group [8] using pulses of width 300 μs, current of 2 mA and a frequency of 12 cycles per minute. The subject chosen was a 29-year-old insulin-dependent diabetic woman with symptomatic gastroparesis, and the results showed improvement in her symptoms, as evidenced by recurrence with electrode malfunction and reimprovement when another of the simultaneously placed electrode pairs were used to continue pacing. Also gastric entrainment occurred, in addition to an improved gastric emptying rate, although she remained on cisapride throughout the study. A year later, a study on nine patients with severe gastroparesis had a series of 4 mA currents applied with a width of 300 ms and a frequency of 10 % higher than that recorded at baseline [19]. This showed a significant improvement in symptoms, and all nine patients' stomachs were entrained, and had reduced gastric emptying times, with a mean time of 5 min (range 1–10 min) A preliminary report from a trial 2 years previously using a frequency of 12 cycles per minute also showed symptom improvement, but there was no data for gastric emptying times [12]. Again a further study from 1998 revealed immediate improvement in nausea and vomiting, with the possibility of the delayed effect of improved gastric emptying time using the same stimulation characteristics. It is thought that this high-frequency, low-energy combination may exert its effects via neuronal activity rather than true pacing of the slow wave [24] and direct muscle contraction; thus, it is referred to as gastric electrical stimulation. An implantable system was produced, and in 2000 the Enterra™ Therapy System was approved for use in the USA.

How It Works

How the technique brings about a reduction in symptoms is unknown, but is thought to involve a neuronal pathway. The stimulation impulses are too weak to excite gastric smooth muscles, but are able to excite gastric nerves. The possibility that it may exert its effects through a placebo-like action has been disproved by a multicentre double-blind, randomised crossover trial on adults [2]. This year-long trial initially randomised 33 patients (17 diabetic and 16 idiopathic) to a month of the stimulator setting to its 'on' or 'off' mode, followed by a further month in the opposite mode (i.e. 'off' or 'on'). To complete the study, all the pacemakers were set to 'on' for the remaining months to achieve 6- and 12-month follow-up. The results were measured by recording all symptoms using a total symptoms score (TSS; bloating, early satiety, epigastric pain, nausea, postprandial fullness and vomiting, combined with a 5-point severity score for each symptom) and gastric emptying by a low-fat test meal and scintigraphy. They found that there was a significant decrease in vomiting frequency and total symptom score throughout the study regardless of cause, and no association between changes in symptoms and gastric emptying. For children, there is no equivalent trial, and thus far there has only been one published case series of gastroparetic children receiving an implanted GES [13] for intractable nausea.

Implantation

The gastric electrical stimulator generates low-energy stimuli at a frequency of 12 cycles/min (high frequency) that restore myoelectrical activity.

The pacemaker itself looks very much like a cardiac pacemaker, with a similar-sized generator unit. The device is implanted at surgery under a general anaesthetic, using either an upper midline laparotomy or laparoscopic approach. Two electrodes are placed through the serosal surface of the stomach, 1 cm apart, approximately 10 cm from the pylorus, corresponding to the site of the intrinsic pacemaker. During the operation the electrodes, which are attached to button-like pads, are stitched into place using a non-absorbable suture, and a gastroscopy is performed to ensure that their tips have not perforated the mucosa. A lead is attached to each electrode, and the wire is passed through the rectus muscle on either side of the abdomen and into a subcutaneous pocket created to house the generator unit. It is important to make sure that the leads are treated with care and that there are not excessive lengths within the abdominal cavity. The subcutaneous pocket is closed independently of the midline mass closure. The functioning of the unit needs to be checked at various points during the operation to ensure that no dislodgement of the leads has occurred, and also just before and after abdominal closure.

A laparoscopic approach can be used instead of an upper midline laparotomy. The number of ports varies by surgeon preference, employing either three ports (two 5 mm, and one 10 mm port which later is enlarged to house the stimulator) [13], or four (three 5 mm and one 10 mm) [5].

Results: Children

The only published case series in children [13] has only nine cases. Eight were female and one male, and eight were suffering with nausea. Five had idiopathic gastroparesis, two were idiopathic/postviral, and one was postsurgical following operations for oesophageal atresia with tracheoesophageal fistula with her last operation, a redo ileocolic anastomosis 1 year previously. All underwent gastric emptying studies with scintigraphy and EGGs for temporary pacing. The temporary pacing for 2–7 days was performed using endoscopically placed wires which were brought out through the mouth and connected to the stimulator unit. The last five cases also had biopsies taken to analyse for the interstitial cells of Cajal. Results of this small series showed that both nausea and vomiting were reduced with the use of both temporary and permanent pacemakers, and as seen in the adult reports, there was no improvement in gastric emptying times. As seen in adult reports, patients who have abnormal or fewer interstitial cells of Cajal have a poorer prognostic outcome with the pacemaker. In one of the patients, the pacemaker failed within 2–4 months, and in another there was progression of multiple autoimmune diseases (lupus, diabetes mellitus and hypothyroidism). Seven children were able to return to schooling.

Results: Adults

Gastric pacing using high-frequency, low-energy impulses has produced consistent results from different centres. Total symptom scores recorded pre- and post-investigation have shown improvement in vomiting, early satiety, bloating, postprandial fullness, nausea and epigastric pain; however, gastric emptying appears not to be significantly improved by this procedure. There appears to be no direct correlation between gastric emptying times and symptomatic improvement [1, 10, 17]. In a subset of a pacing trial (Gastric Electromechanical Stimulation (GEMS) study group), the nutritional aspect of pacing was considered. Twelve patients between 19 and 48 years (eight women and four men) had their weight, BMI, albumin, cholesterol, complete blood count and route of nutrition recorded at baseline, 12 months, 24 months and 5 years. The weight and BMI increased to a statistically significant level, but although their biochemistry improved, it was not to a significant level beyond 6 months.

There are few studies providing long-term data, but it has shown that symptoms remained significantly lower up to 3 years following insertion, and patients retained their weight gain [18].

Complications of Pacemakers

The commonest complication of pacemakers is infection within the pocket necessitating its removal, and can occur at any time following implantation [1, 10, 18]. This may be due to malnutrition, the systemic complications of diabetes and the wound being situated near a stoma site. In one instance, trauma to the skin overlying the pacemaker resulted in its extrusion and removal [13]. Other rarer complications are small bowel volvulus around the leads, and the pacemaker switching itself off. This latter complication manifested itself by patients returning to hospital complaining that their symptoms had returned. It is thought to have been caused by electromagnetic fields produced by strong magnets such as the ones found in airport scanners, department stores and loudspeakers [9].

Conclusion

GES has produced some fairly consistent results from nearly a decade of data from the implantable unit. Patients do experience fewer debilitating gastrointestinal symptoms and admissions to hospital, are less dependent on jejunal feeding and parenteral nutrition and have a better quality of life.

The question surrounding how it mediates its effects remains to be answered, and there is still very little data regarding the use of the device in children. In addition, there are no long-term follow-up results for the only published case series of nine children.

More long-term research needs to be undertaken, including the effects on children.

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Dermatology and the Oesophagus 130

Sue Protheroe

Diseases of the skin and oesophagus coexist more frequently than could be expected by chance. This could be explained by similar functions and origin of both these organs. They both provide a protective layer and interface with the external environment being first point of contact with infective, irritant, or allergenic agents. Both the organs are lined by stratified squamous epithelium that contains immunocompetent antigen-presenting cells. Structurally, the oesophageal wall is composed of four layers: innermost mucosa, submucosa, muscularis propria, and adventitia. Oesophageal mucosa is nonkeratinized stratified squamous epithelium except at the gastroesophageal junction (GEJ), where squamous epithelium joins the columnar epithelium of the gastric cardia. Unlike the remainder of the GI tract, the oesophagus has no serosa. The basal cell layer (BCL) makes up approximately 20 % of the epithelial layer and is lined by lamina propria (LP), which is a thin layer of connective tissue.

Several types of interaction between the skin and the oesophagus are possible. The awareness of association between these organs is important as it not only helps in establishing a diagnosis but also helps in anticipating and recognising complications associated with them.

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The common interactions include:

1. Dermatological manifestations of a primary gastrointestinal (GI) disease
2. Oesophageal involvement in a primary skin disease
3. A common pathology affecting both organs (Table 130.1)

Recognition of this association between oesophageal and skin disease is important in identifying the common pathology. Early Diagnosis is possible when identifying dysphasia in children with personal or family history of a skin condition. The correct diagnosis of such conditions relies on the ability of the gastroenterologist to recognise the underlying dermatologic disorder (Table 130.2).

Since the neuromuscular anatomy of the proximal and distal portions of the oesophagus is different, various diseases can affect either the skeletal or smooth muscle portions of the oesophagus. The upper third consists of muscularis propria, and the upper oesophageal sphincter (UES) is skeletal muscle and innervated by the central nervous system via vagal and the recurrent laryngeal nerves. There often are overwhelming symptoms of dysphagia and odynophagia because of involvement of striated muscle of the oesophagus or oropharynx. Muscular diseases affecting the striated muscle include muscular dystrophies (myotonic and oculopharyngeal, the former presenting more

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Table 130.1 Diseases affecting the skin and the oesophagus

1. Collagen vascular disorders
(i) Systemic sclerosis
(ii) Dermatomyositis
(iii) Systemic lupus erythematosus (SLE)
2. Graft-versus-host disease
3. Oro-cutaneous-genital syndromes
(i) Stevens-Johnson syndrome
(ii) Behcet's disease
4. Hyperkeratotic disorders
(i) Acanthosis nigricans
(ii) Darier's disease
(iii) Lichen planus
5. Bullous disorders
(i) Epidermolysis bullosa
(ii) Pemphigus
6. Inflammatory disorders
(i) Crohn's disease
7. Infections
(i) Herpes simplex
(ii) Chickenpox
(iii) Human immunodeficiency virus

Table 130.2 Skin lesions seen associated with oesophageal disease

Hyperpigmentation	Acanthosis nigricans
	Darier's disease
	Lichen planus
Vesicular or pustular rash	Herpes
	Chickenpox
Bullae	Epidermolysis bullosa
	Pemphigus
Macular or papular rash	Graft-versus-host disease
Erythematous rash	Dermatomyositis
	GVHD
Erythema nodosum	Crohn's disease
Angular cheilitis, glossitis, koilonychias	Sideropenic dysphagia – Plummer-Vinson syndrome [65]
Febrile neutrophilic dermatosis	Sweet's syndrome

often in children, although relatively rare) and inflammatory myopathies (e.g. dermatomyositis, polymyositis, and inclusion body myositis).

The distal third of the oesophagus and lower oesophageal sphincter is composed of smooth muscle which is aligned in a circular fashion. Smooth muscle is innervated by the autonomic nervous system which involves neurons in the myenteric plexus of the wall. Scleroderma causes abnormalities of the autonomic nervous system, microvasculature, and immune system and causes smooth muscle atrophy and fibrosis. The middle third of the oesophagus is a mixture of both types of muscle (transition zone).

Collagen Vascular Diseases

Systemic sclerosis (SSc) or scleroderma is a connective tissue disease and one of the most important secondary motor disorders to affect the oesophagus. The proximal one-third of the oesophagus, with its striated muscle, is spared. SSc causes abnormalities of the autonomic nervous system, microvasculature, and immune system. Atrophy of the smooth muscle layers of the muscularis propria characterises oesophageal involvement. It is accompanied by varying degrees of tissue fibrosis and chronic inflammatory infiltration in numerous visceral organs, prominent fibroproliferative vasculopathy, and humoral and cellular immune alterations. Juvenile systemic sclerosis, although rare, accounts for 5% of all cases [55]. It is more likely to occur in children between 10 and 16 years, is common in females as compared to males, and is equally distributed across all races [18].

Skin disease is in the form of skin tightness and induration with hypo- or hyperpigmentation. The skin of the hands may be oedematous or swollen early in the disease and precedes the indurated sclerotic stage. In the sclerotic phase, the skin may appear tight and shiny, with a characteristic loss of hair, decreased sweating, and loss of the ability to make a skin fold. This process of thickening generally begins distally on the fingers and progresses proximally in a continuous symmetrical fashion.

The gastrointestinal tract is frequently affected in diffuse and limited disease. Although any part of the gastrointestinal tract can be involved,

oesophageal disease occurs in nearly all patients. Patients may have no symptoms and simply present with features of the connective tissue disorder. Oesophageal involvement leads to reflux symptoms including heartburn and acid regurgitation reported in up to 50 %. Smooth muscle atrophy and fibrosis of the distal two-thirds of the oesophagus result in diminished peristalsis. The extent of the resulting hypomobility can vary from occasional uncoordinated contractions to complete paralysis [1]. Reflux, seen in 40 % of the cases, is a result of low pressure in lower oesophageal sphincter and disturbed peristalsis. This causes reflux oesophagitis and dysphagia in 1.5–13 %, though the severity of these symptoms is not related to degree of oesophagitis [14]. Dysphagia is possibly due to hypotensive oesophageal contractions or non-peristaltic contractions, but it more commonly relates to superimposed stricture formation or oesophageal inflammation, which results in loss of compliance of the distal oesophagus.

The x-ray findings in scleroderma oesophagus may sometimes be confused with achalasia as both may show a dilated oesophagus with narrowing at the GEJ. However, endoscopic and manometric findings can differentiate the two quite easily [17]. Manometric studies in juvenile localised scleroderma reveal that oesophageal involvement occurs even in the absence of specific symptoms [24]. Candida oesophagitis is a complication of SSc not seen with non-SSc reflux and is due to poor emptying of the oesophagus, immunosuppressive therapy, and acid suppression predispose [21]. Long-term complications include strictures, found in 17–29 % of adults. Most patients with oesophageal involvement with scleroderma have associated Raynaud's phenomenon. Respiratory symptoms may also occur, owing either to direct lung involvement with scleroderma or to aspiration.

Treatment of gastroesophageal reflux in SSc includes behavioural modification and medical therapy, mainly with proton pump inhibitors and prokinetic agents. Surgical intervention has only a limited role in management [44].

Systemic lupus erythematosus (SLE) is an autoimmune connective tissue disease of the small vessels. It is more common in girls with the peak age of incidence between 14 and 17 years. Dysphagia occurs in up to 13 % of adults with SLE and heartburn in up to 50 %. Oesophagitis with ulceration has been observed in 3–5 % and oesophageal perforation may rarely occur. Reduced oesophageal motility has been demonstrated in up to 72 % of adults with SLE [11], and although the motility disorder is mostly mild, aperistalsis has been reported up to a fourth of the patients [25]; the symptoms of dysphagia is worsened by gastroesophageal reflux and secondary candidiasis.

Treatment of dysphagia is systemic control of inflammation with corticosteroids and non-steroidal anti-inflammatory agents. The use of prokinetic agents and proton pump inhibitors has also been shown to be helpful in reducing symptoms [27].

Dermatomyositis

Inflammatory myopathies are acquired muscle diseases which include polymyositis and dermatomyositis. The dysphagia associated with these myopathies primarily affects the skeletal muscle-activated oropharyngeal phase of swallowing and may precede weakness of the extremities or present as the sole symptom [63].

Dermatomyositis is an idiopathic inflammatory microangiopathy affecting the skin and muscles characterised by progressive proximal symmetrical weakness, elevated levels of muscle enzymes, and cutaneous lesions. The pathognomonic features include heliotrope rash, a symmetrical erythematous rash involving the periorbital region, and Gottron papules: papules and plaques found over bony prominences, particularly the metacarpophalangeal joints, the proximal interphalangeal joints, and the distal interphalangeal joints. Other skin changes include malar erythema, violaceous erythema, and poikiloderma. Gastrointestinal involvement is seen in 5 % of children and up to 40 % during the course of the disease due to underlying vasculopathy or impairment of muscle function. Dysphagia is the most common symptom.

One-third of affected children have oesophageal disease [47], which mainly involves the striated muscles of the oesophagus (as in the rest of the body), but up to two-third of affected patients have dysfunctional motility in the distal oesophagus, implying involvement of smooth muscles as well [26]. Vasculitis also leads to inflammatory changes.

Dysphagia as a result of abnormal motility and reflux may be the presenting feature of the disease, but the diagnosis may not be apparent until the dermatologic disease is clearly observed [64]. There is a direct correlation between GI symptoms and the severity of peripheral skeletal muscle weakness [21]. Vascular changes can cause ulcerations in the oesophagus rarely leading to perforation [16].

Barium contrast studies reveal a dilated oesophagus with reduced peristaltic movements and gastroesophageal reflux in 30–50 % of cases [34]. Oesophageal manometry can also be used in selected cases.

A variety of medical, rehabilitation, and interventional treatments are used to manage inflammatory myopathies-associated dysphagia. Medical treatment emphasises control of the disease process, whereas rehabilitation focuses on swallowing compensation techniques, exercises, and diet modification. Most commonly used pharmacological agents are systemic corticosteroids. Other medications used for this purpose include azathioprine, methotrexate, cyclophosphamide, cyclosporine, mycophenolate mofetil, tacrolimus, rituximab, IVIG, or plasmapheresis [64].

Graft-Versus-Host Disease

The oesophageal epithelium, like skin and mucous membranes, is a target organ in chronic graft-versus-host disease.

Graft-versus-host disease (GVHD) is an immune-mediated disease resulting from a complex interaction between donor and recipient adaptive immunity. The main effectors in GVHD are immune-competent donor T cells in the grafted organ.

GVHD can be acute if it occurs within the first 100 days or chronic, if it occurs after this period. Acute GVHD occurs in 35–50 % of children after haematopoietic stem cell transplant and less frequently after solid organ transplant. The three main organs involved include skin, liver, and gastrointestinal tract. The earliest manifestation is skin GVHD which is in the form of a maculopapular rash that often starts with the palm and sole but can involve any part of the body.

The gastrointestinal involvement of acute GVHD is in the form of enterocolitis. It can sometimes affect the oesophagus presenting as anorexia, dyspepsia, food intolerance, nausea, and vomiting in children [5] due to desquamative oesophagitis with web formation. Mucosal oedema, hyperaemia, and widespread sloughing are seen, and severe cases may present with bullous lesions of the oesophagus.

Diagnostic endoscopy and disruption of webs should be performed carefully to avoid perforation. Treatment should be directed toward suppressing the underlying immunologic disorder and at preventing acid-peptic reflux.

Chronic GVHD presents 100 days after the transplant. Skin changes are the commonest presentation and can be lichenoid and sclerodermatous [6]. Lichenoid type, characterised by epidermal atrophy and irregular acanthosis, predominates early in the course of chronic GVHD. Sclerodermatous form appears late, usually 6–12 months after transplant. It is insidious in onset and can be in the form of localised plaques on the trunk or over pressure areas or widespread involvement.

Involvement of the oesophagus in chronic GVHD is seen in about a quarter of the patients and presents as dysphagia, weight loss, and retrosternal pain. Oesophagitis and desquamation of the mucosa can lead to development of webs and strictures. Strictures though not common can be seen in 7 % of children with dysphagia symptoms [56]. Prompt recognition of oesophageal disease and institution of immunosuppressive therapy dramatically alters the natural history of this disease [39]. The radiographic findings of 14 symptomatic patients with chronic GVHD involving the oesophagus were reviewed and found to

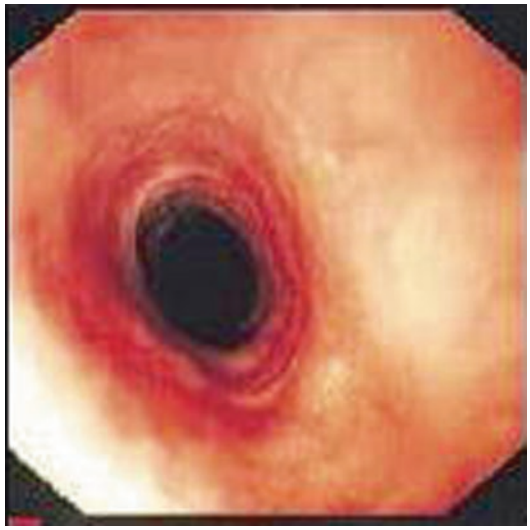

Fig. 130.1 Graft-versus-host disease. Desquamation and fibrosis are seen characteristically in chronic GVHD

have webs, ring-like narrowing, and tapering strictures in the mid- and upper oesophagus [39].

Endoscopic examination is the most important investigation and shows mucosal desquamation most pronounced in the upper part. Changes of chronic inflammation and resultant strictures or webs can also be seen. A fifth of the patients with oesophageal symptoms could have normal endoscopic appearances, and the diagnosis is confirmed by characteristic histological changes on biopsy [62]. The specific histological features of oesophageal involvement include the presence of epithelial single-cell necrosis which may or may not be accompanied by increased inflammation and reactive epithelial changes or loss. Ulceration and submucosal fibrosis reflect long-standing disease but are not specific features of oesophageal GVHD [48] (Fig. 130.1).

Acute GVHD of GI tract responds promptly to immunosuppressive therapy. The most commonly used treatment is systemic corticosteroids. For children who are refractory to treatment with steroids, alternatives used are infliximab, rituximab, and antithymocyte globulin (ATG). Maintenance of nutrition is just as important as immunosuppressive therapy, and early immunosuppression and nutritional therapies have shown to be associated with improved outcome [18]. Response to immunosuppression is not effective in children with chronic GVHD, and various steroid-sparing agents are used to minimise the side-effects of long-term corticosteroid therapy. Management of oesophageal strictures is by dilatation, although the risk of recurrence of stricture remains high [36].

Oro-Oculo-Genito-Cutaneous Syndromes

Behcet's Disease

Behcet's disease (BD) is a multisystem disorder characterised by aphthous ulcers, genital ulcers, and eye lesions. The primary lesion is vasculitis which mainly involves the small vessels. The pathogenesis of BD is unknown, genetic susceptibility may be present, and the disease may be triggered by infection. It is more common in males of Asian or Mediterranean descent, and only 1–2 % of the affected patients with BD are in the paediatric age group [45]. Neutrophilic hyperfunction and infiltration of lesions by neutrophils is characteristic. This forms the basis of tests which is formation of a neutrophil-rich pustule at the site of needle prick to the skin. Painful recurrent oral ulcers are the most common-presenting feature with other symptoms being genital ulcers, posterior uveitis, and skin lesions. Skin lesions are in the form of erythema multiforme, papulopustular lesions, ulcers, erythema nodosum, thrombophlebitis, or necrotizing vasculitis.

Gastrointestinal involvement is seen in 50 % of cases and mainly involves the small or the large bowel. Oesophageal involvement is rare and is in the form of ulceration, erosions, and widespread oesophagitis [41]. Ulcers are typically longitudinal and present in the middle part of the oesophagus. They are usually deep tunnelling ulcers and can lead to stricture formation. Histology shows features of nonspecific inflammation with neutrophilic infiltration.

Treatment is with immunosuppressive medications like systemic corticosteroids though steroid-sparing agents like azathioprine, cyclosporine, and anti-TNF agents are increasingly

being used [35]. 5-ASA medications, by virtue of their anti-inflammatory effects, are also effective in treating oesophageal disease associated with Behcet's disease [60].

Stevens-Johnson Syndrome (SJS)

SJS is an inflammatory disorder that predominantly involves the skin and mucous membranes and is triggered by an allergic reaction to certain drugs such as sulphonamides, tetracycline, amoxicillin, and ampicillin. Skin involvement starts as erythematous macular rash which is followed by epidermal detachment which involves up to 10 % of the total skin surface area. Ocular involvement at the onset of disease is frequent and can range from acute conjunctivitis, eyelid oedema, erythema, crusts, and ocular discharge to conjunctival membrane or pseudomembrane formation or corneal erosion. The Nikolsky sign is positive if mechanical pressure induces epidermal detachment, but is not specific for SJS. Abnormal laboratory findings may include an elevated sedimentation rate, hypoalbuminemia, elevated liver enzyme levels, microscopic haematuria, and mild leukocytosis. Mucosal involvement in the form of erythema and erosions is seen in up to 90 % of cases. The commonest site involved is the oral and genital mucosa, and in some cases the respiratory and gastrointestinal tracts are also affected [50].

Oesophageal disease manifests as dysphagia and retrosternal pain. Lesions involve the mucosal lining of the entire oesophagus, with blistering of the epithelium and formation of large ulcers. There is sloughing of mucosa which can cause gastrointestinal bleeding. Usually there is complete healing of the lesions of the gastrointestinal tract, but rarely there can be cicatrisation with formation of stricture [12].

Treatment is in the form of withdrawal of the causative agent and supportive therapy in the form of nutrition and fluid and electrolyte management. There is some data supporting the use of intravenous immunoglobulin, though they are not in general use currently in the treatment of SJS [49].

Hyperkeratotic Disorders

Acanthosis Nigricans

Acanthosis nigricans (AN) is caused by factors that stimulate epidermal keratinocyte and dermal fibroblast proliferation. In the benign form of acanthosis nigricans, this factor is probably insulin or insulin-like growth factor (IGF). Other proposed mediators include epidermal growth factor receptor [EGFR] or fibroblast growth factor receptor [FGFR]. Familial and syndrome forms of AN have been identified. Many syndromes share common features, including obesity, hyperinsulinism, and craniosynostosis.

Acanthosis nigricans is more common in people with darker skin pigmentation, with prevalence in whites less than 1 % in whites less than 1 % [42], but has no sex predilection [58]. Patients usually present with an asymptomatic area of darkening and thickening of the skin. Lesions begin as hyperpigmented macules and patches and progress to palpable plaques. Histological examination reveals hyperkeratosis, papillomatosis, with minimal or no acanthosis, or hyperpigmentation. The dermal papillae project upward as finger-like projections, with occasional thinning of the adjacent epidermis.

Acanthosis can also involve the oesophagus which is in the form of granular nodules through the length of the oesophagus. Small irregular lining of the oesophagus can be seen in upper GI contrast, and endoscopy shows multiple papillary-protruded lesions with white apices in the entire oesophageal mucosa. Histological features of these lesions are epithelial hyperplasia and papillomatosis [40]. AN increases the risk of developing oesophageal carcinoma in adulthood.

Darier's Disease (Keratosis Follicularis)

Keratosis follicularis is an autosomal dominant inherited disease characterised by hyperkeratotic papules in seborrheic regions. The underlying defect resides with a disorder of cytoskeletal

tonofibrils and desmosomes. A mutation in the long arm of chromosome 12 (ATP 2A2 gene) has been implicated [52]. Abnormal keratinocyte-keratinocyte adhesion and aberrant epidermal keratinisation are the primary histological features of keratosis follicularis. Electron microscopy reveals loss of desmosomes, breakdown of desmosome-keratin intermediate filament attachment, and perinuclear aggregates of keratin intermediate filaments. It usually presents in the first or second decade of life and both sexes are equally affected [45]. The severity of disease can vary considerably between individuals with some being asymptomatic and others having extensive lesions. The skin lesions are characterised by hyperkeratotic papules and plaques primarily in seborrheic areas of the face, neck, and trunk. Small palmoplantar pits are very characteristic of Darier's disease.

Mucosal lesions are detected in approximately 15 % of patients and are found most commonly in the oral cavity or anogenital region. They are in the form of white papules with a central depression [9]. Though rare there are few reported cases of involvement of oesophageal mucosa and association with malignant change in adulthood [2].

Lichen Planus

Lichen planus is a subacute to chronic mucocutaneous disorder of unknown aetiology which in its classical presentation involves the oral cavity and skin. It affects both genders with equal frequency and can affect any age group. Cutaneous lichen planus is characterised by eruptions of violaceous, scaling papules and plaques. These plaques typically are intensely pruritic and are most commonly localised to the extensor surfaces of the forearms and legs. Lichen planus of the mucosal surfaces may include lesions of the perineum, pharynx, and oesophagus. Mucosal involvement coexists with skin lesions in approximately 30–50 % of patients, but can occur as the sole manifestation of disease [3]. Involvement of the oesophagus by lichen planus is a well described and is seen in up to 25 % of cases [8]. Correct diagnosis of oesophageal lichen planus is critical to distinguish from other more common causes of oesophagitis because of its tendency to cause persistent dysphagia and stricture formation.

Early symptoms are mainly of dyspepsia and heartburn. If left untreated, it develops into dysphagia resulting from oesophagitis and stricture formation. Due to lack of recognition of association between skin and oesophageal lesions, diagnosis is usually delayed, and patients are treated with antireflux medications [30]. Recognition of oesophageal lichen is important to prevent complications like stricture formation. Stricture dilatation, without concomitant medical treatment, can exacerbate extra-oesophageal disease in a Koebner-like phenomenon [20]. There is also a potential risk of malignant transformation to squamous cell carcinoma.

Endoscopic features of lichen are in the form of hyperkeratotic papules, nonspecific oesophagitis, and strictures in late stages. The risk of malignant transformation is currently unknown but may parallel that of oral lesions at approximately 1–3 %.

Histology shows band-like inflammatory infiltrate with a predominance of mature T cells and parakeratosis (Fig. 130.2).

Treatment is with immune-suppressive agents like corticosteroids, cyclosporine, and azathioprine. Retinoids have also been used for cutaneous lesions. Although most patients in the literature who have oesophageal lichen planus have been reported to show clinical improvement with these agents, relapse can be expected when treatment is discontinued [8].

Plummer-Vinson or Paterson-Kelly syndrome presents as a classic triad of dysphagia, iron-deficiency anaemia, and oesophageal webs and, although rare, has been described in children and adolescents [43]. Other signs may be glossitis, cheilitis (scaling and fissures at corners of mouth due to riboflavin deficiency), and nail changes. Patients are at an increased risk of postcricoid squamous cell carcinoma [4].

The pathogenesis of this condition is not known and may be due to iron and nutritional

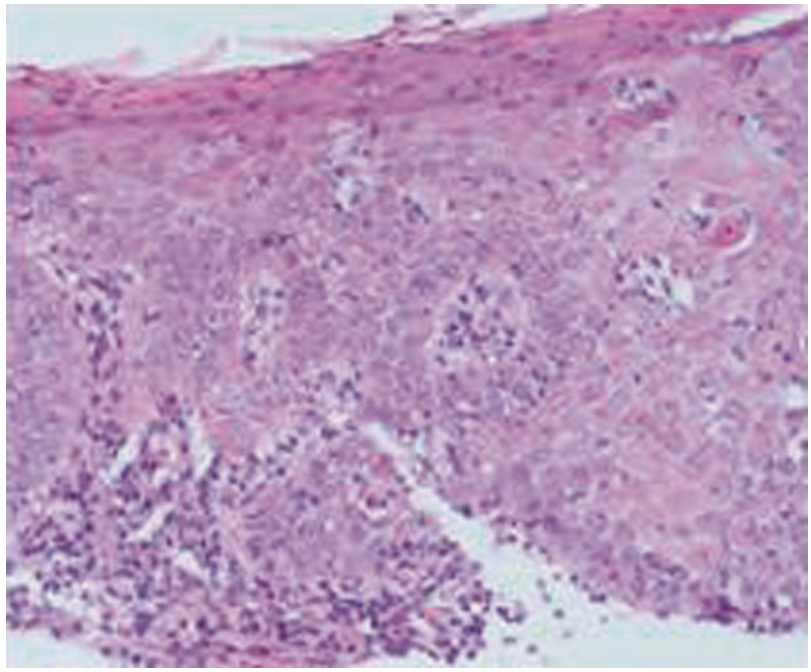

Fig. 130.2 Lichen planus. Squamous epithelium of the oesophagus showing lymphocytic infiltration and Civatte bodies

deficiencies and autoimmune factors in genetically predisposed individuals. The most important aetiological factor is iron deficiency and resulting anaemia, possibly based on decreased constricting power of the pharyngeal musculature due to impaired oxidative metabolism in the striated musculature, but other possible factors are malnutrition and perhaps autoimmunity. The dysphagia is worsened by formation of webs.

Treatment is with iron supplementation to correct deficiency. This usually is adequate to correct dysphagia except in cases with webs where oesophageal dilatation may be required. These patients would also need periodic monitoring for oesophageal carcinoma. The incidence of this condition is reducing which may be due to better diets and the treatment of sideropenic anaemia with inorganic iron salts [13].

Sweet's syndrome, also known as febrile neutrophilic dermatosis, can occur in children and has been reported in adult patients with underlying malignancy, including adenocarcinoma of the oesophagus [59].

Bullous Disorders

Epidermolysis Bullosa

Epidermolysis bullosa (EB) is a group of inherited disorders characterised by the formation of blisters spontaneously or after minor skin trauma. An estimated 5,000 and 12,500 people are affected in the United Kingdom and United States, respectively [19]. It results from the mutations of genes encoding for structural proteins located at the junction between the epidermis and the dermis. In normal individuals, there are "anchors" between the two layers that prevent them from moving independently from one another. In people born with EB, the two skin layers lack the anchors that hold them together, and any action that creates friction between the layers (like rubbing or pressure) will create blisters and painful sores.

There are three major types of EB, simplex, dystrophic and junctional. These vary from relatively mild to incapacitating, crippling, and sometimes fatal disorders. Within these there are

over 20 different subtypes of EB, each with their own characteristic symptoms.

The transmission of EB can be dominant or recessive, with recessive form being associated with more severe diseases. It is divided into three categories, epidermolysis bullosa simplex, junctional epidermolysis bullosa, and dystrophic epidermolysis bullosa.

The skin lesions in the recessive form start within the first few months of life. They are in the form of tense, fluid-filled blisters, erosions, or crusts. Areas prone to blistering due to pressure, trauma, or excessive heating include the fingers, hands, elbows, feet, legs, and diaper area. Scarring is often seen associated with these lesions [33].

EB frequently involves the gastrointestinal (GI) tract and may lead to poor dentition, oesophageal strictures, malabsorption, severe constipation, and anal fissures. The commonest areas involved are oral cavity, the oesophagus, and anal margin. Oral lesions with resultant scarring cause microstomia [28].

Oesophageal injury is due to the mechanical shearing force of the ingested food. It mainly affects the upper third and is in the form of bullous lesions which can easily rupture. Where there is rupture of bullae, the healing is with scar formation, and this can result in structuring of the oesophagus. There is also associated mucosal damage because of reflux secondary to low pressure in lower oesophageal sphincter. As the skin lesions are characteristic of EB, endoscopy does not add to the diagnosis and can cause further damage by mechanical trauma.

The mainstay of treatment of oesophageal disease is supportive. It is important to minimise trauma which is why soft diet is recommended. Gastrostomy feeding is an effective way of reducing damage and should be considered early in treatment. In view of associated gastroesophageal reflux, antireflux treatment helps minimise mucosal damage. Identification of strictures can be done by upper GI contrast studies and treatment is by balloon dilatation. Those who require frequent dilatations remain on ranitidine or omeprazole for indefinite periods [10]. Gene therapy in the form of transplantation of genetically modified epidermal stem cells to improve the adhesion properties of primary keratinocytes is being investigated as a definitive treatment [37].

Pemphigus

It is a chronic intraepidermal vesiculobullous autoimmune disease involving the skin and mucous membrane. The two main types are pemphigus vulgaris (PV) and pemphigus foliaceus (PF). Childhood pemphigus is a rare disease [15] and constitutes a minority of all the immunobullous disorders in childhood [29]. The mean age of onset in children is 12 years. Mucosal involvement is the first feature followed by cutaneous bullae. Oral mucosa is most commonly involved with blisters and erosions present in 50–70 % of patients [42]. Other mucosal surfaces involved may be the conjunctiva, oesophagus, anus, and genital and nasal mucosa. The primary skin lesion of pemphigus is flaccid vesicles on erythematous or normal skin which breaks easily to form erosions and crust.

Oesophageal disease presents as dysphagia and odynophagia. Typical mucosal lesions are in the form of flaccid bullae and erosions, and the mucosal lining may be detached. Histological examination shows severe inflammation and acantholysis of cells [53]. Strictures can form with long-standing disease and usually present in third to fourth decade of life [53].

The treatment is with high-dose systemic steroids. Other therapies include erythromycin, chloroquine, methotrexate, sulfapyridine, azathioprine, and hydroxychloroquine. A majority of children remain in remission either off medication or low maintenance dose within 1 year regardless of the type of therapeutic intervention used [14].

Crohn's Disease

Crohn's disease (CD) can involve any part of the gastrointestinal tract and is characterised by transmural inflammation of the affected part of

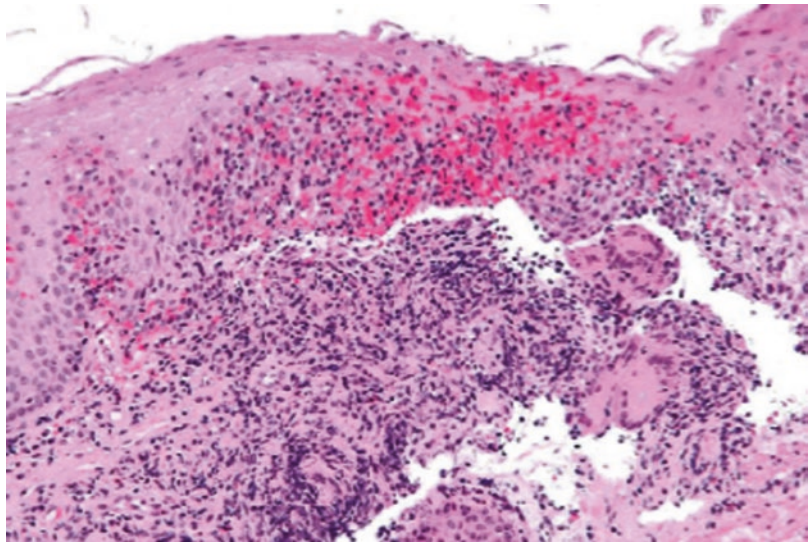

Fig. 130.3 Oesophageal involvement in Crohn's disease

the gut. The incidence of inflammatory bowel disease in the UK according to the British Paediatric Surveillance Unit (BPSU) was 5.3 per 100,000 children, of whom 60 % had CD. Oesophageal involvement is seen in 16 % of children with CD [54] (Fig. 130.3). Approximately, 7–24 % of affected children experience extraintestinal manifestations, of which dermatologic lesions are the second most common [57]. Symptoms of oesophageal disease include odynophagia, dysphagia, and heartburn. Aphthous ulceration is the usual finding of oesophageal CD with biopsies showing characteristic inflammation with or without granulomata. Sometimes linear serpiginous ulcers with cobblestoned mucosa can also be seen. Dermatologic lesions commonly associated with CD and may be as high as 34 % [23] and include erythema nodosum, pyoderma gangrenosum, and cutaneous CD. Less common manifestations are oral-facial granulomatosis, and inflammatory erythema nodosum, an acute, nodular, erythematous eruption seen in the extensor aspects of the lower legs, occurs in as many as 15 % of patients with CD [32]. Pyoderma gangrenosum is seen mainly in ulcerative colitis but also in some cases with CD. It is characterised by a deep ulceration with a violaceous border that overhangs the ulcer bed. These lesions of pyoderma gangrenosum most commonly occur on the legs, but may occur anywhere on the body.

Treatment of these dermatologic conditions is empiric and involves primarily topical and systemic corticosteroids and immunomodulatory agents. Miscellaneous associations include finger clubbing and vitiligo. Cutaneous manifestations secondary to disease complications include vitamin and micronutrient deficiency as a result of malabsorption – stomatitis, glossitis, angular cheilitis (iron and vitamin B), purpura (vitamin C and K), and acrodermatitis enteropathica (zinc). Cutaneous manifestations due to treatment include drug eruptions.

Infections

Human herpesvirus oesophagitis is a well-known infectious complication of patients with an impaired immune system and has also been described as a self-limiting illness in immunocompetent patients [51]. Reactivation of varicella-zoster virus (VZV) as herpes zoster is a well-recognised cause of morbidity in the HIV-infected host: other described complications are ocular, neurological, and chronic atypical skin lesions [22]. No cases of oesophagitis and spontaneous oesophageal perforation caused by VZV have been reported.

Herpes Simplex Oesophagitis

Herpes oesophagitis is more common in immunocompromised children but is an underrecognised condition in the immunocompetent child [6, 65]. It presents either as a primary herpes simplex virus (HSV) infection or reactivation. Fever, odynophagia, vomiting drooling, irritability, and retrosternal pain are presenting features. These symptoms may not be diagnostic, leading to a difficult and delayed diagnosis, unless exposure to HSV disease has been described or skin and/or oropharyngeal lesions are recognised. Endoscopy typically shows erythema and ulcers mainly in the distal and mid-oesophagus, but at times, the disease affects the entire oesophagus. Appearances can mimic the burns caused by caustic soda ingestion in children. Herpes oesophagitis is manifested by the development of small vesicles that subsequently rupture to form discrete superficial ulcers on the mucosa. In immunocompetent patients, the host response promotes healing of the ulcers, but in patients who are severely immunocompromised, the condition may progress from discrete areas of ulceration to a diffuse hemorrhagic oesophagitis or perforation. Histological examination shows inflammation with intranuclear inclusions present in about half of the cases [7]. Culture and PCR are the most specific tests for diagnosis and should be performed in all suspected cases [38].

Treatment of herpes oesophagitis in immunocompromised individuals is with acyclovir. In immunocompetent patients, its role is doubtful, and there is some adult data supporting its use as it reduces the duration and severity of symptoms [31].

Other causes of herpes virus oesophagitis in patients with human immunodeficiency virus (HIV) infection have been reported due to cytomegalovirus (CMV) and herpes simplex virus types 1 and 2 (HSV 1/2).

Varicella Zoster

Typically, varicella-zoster infection remains cutaneous, although visceral involvement has been described especially in immunocompromised patients. Varicella oesophagitis is a rare complication. In immunocompetent children, it is self-resolving, but in immunocompromised individuals, it can cause blistering lesion which can form ulcers [61].

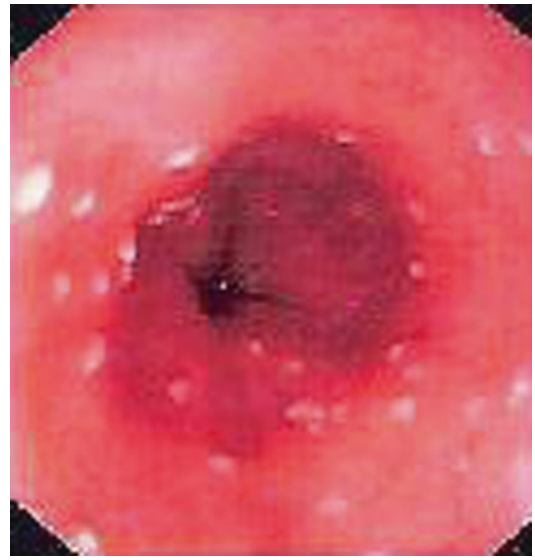

Fig. 130.4 Oesophageal candidiasis

Oesophageal Candidiasis (Fig. 130.4)

Opportunistic oesophageal infections may occur in HIV-positive patients, who may manifest other skin lesions like Kaposi's sarcoma [46]. Kaposi's sarcoma is a neoplastic disorder of endothelial cell proliferation that occurs most frequently in the skin associated with the HIV virus, and gastrointestinal lesions are common.

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