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Nikhil Thapar
Carlo Di Lorenzo
Editors

Pediatric Neurogastroenterology

Gastrointestinal Motility and Functional Disorders in Children

Second Edition

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To my parents with love.

Christophe Faure

To my parents for their unconditioned support and love.

Carlo Di Lorenzo

To my beloved father Baldev Sahai Thapar—blessed by your and mum's unending love, forever my guiding light and inspiration.

Nikhil Thapar

To our patients and all the children afflicted by motility and sensory digestive disorders.

Christophe Faure
Carlo Di Lorenzo
Nikhil Thapar

Foreword

Neurogastroenterology is certainly not an arcane or secretive branch of medicine. Still, if one were to judge from the proportion of physicians who are knowledgeable about the subject, especially in its pediatric version, one might come away with the idea that the tenets of neurogastroenterology are imparted only to initiates who are sworn to secrecy in midnight rituals over pots filled with boiling entrails. In fact, Nikhil Thapar, Carlo Di Lorenzo, and Christophe Faure have succeeded masterfully in dispelling this aura of mystery in their wonderful textbook *Pediatric Neurogastroenterology*, which is now entering its second edition. There is no longer an excuse for medical ignorance. Pediatric neurogastroenterology is laid out clearly, logically, and encyclopedically for anyone who has mastered and enjoys the art of reading. The chapters are chosen to make the field approachable and significantly, in an age where clinical understanding has to compete with insurance companies for doctors' attention, clinically relevant. The authors of individual chapters are authorities, which is to be expected, but many are more than that. They are truly the leaders to whom other authorities direct their questions, and they are so because they are the actual discoverers of many of the answers.

It has always seemed to me to be to be axiomatic that there is too much known about any field of medicine to be able to encompass all of it as a single compendium of facts. Indeed, those textbooks that try to do this tend to read like dictionaries, to become dated almost before they appear in print, and to be, in a word, useless. Valuable textbooks, like this one, deal with concepts and understanding. They present logical frameworks in which normal anatomy and physiology make the pathophysiology of a kaleidoscopic variety of disorders comprehensible and therefore easily learnable. If the structural/functional flaws that give rise to disease can be understood, then diagnosis, prognosis, and treatment become logical and easily learned. Pithy sentences, rhymes, and words put to music are much more readily committed to memory than a series of unrelated words or phrases. This textbook of pediatric neurogastroenterology uses the basic science of neurogastroenterology as the music that makes the medicine, not just a good read but a retainable one as well.

The editors, of course, are distinguished scientists and clinicians. They have recruited an admirable list of cowriters to do individual chapters. It is impossible to mention all of them, but it would be hard to find a better person than Alan J. Burns to write about the development of the enteric neuromuscular system. Alan traces his training back to Nicole Le Douarin who, with Alan at her side, brought on the modern understanding of the development of the enteric nervous system from the neural crest. One person who might have done as well is the author of the chapter about Hirschsprung's disease, Robert Heuckeroth, who probably understands that condition and knows more about it than Hirschsprung, who lacked the background knowledge that Alan J. Burns has provided in his earlier chapter. These chapters all fit well with that of Cheryl Gariepy on the genetics of motility disorders and Nikhil Thapar on the future with cell-based therapies. All told, this is a great textbook that should bring all of pediatrics up to speed with its neurogastroenterological branch and all of adult neurogastroenterology up to speed with its pediatric branch.

New York, NY, USA

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Preface to the First Edition

In the past 20 years, major advances have been achieved in the care of children with pediatric gastrointestinal motility and sensitivity disorders. This is a reflection of the progress that has been made understanding such conditions at the developmental and molecular level as well as the development of novel tools to investigate and treat them. These progresses have led to the birth of a new "science," namely, *neurogastroenterology*, which is devoted to "study the interface of all aspects of the digestive system with the different branches of the nervous system" and which has now established itself as a major area of clinical practice and research. In the past two decades, there has been an almost exponential increase in publications of scientific papers in the field, a plethora of international fora for the discussion of such conditions and creation of dedicated journals with respectable citation indices. Pediatric neurogastroenterology and motility has not lagged behind and arguably is fast becoming a major and popular subspecialty in its own right.

With this book, we aimed to draw upon an extensive international expertise to provide a contemporary state-of-the-art reference textbook for pediatric neurogastroenterology and motility that both specialists and generalists alike will find helpful.

Overview of the Book

The first chapters are dedicated to some of the success stories of the field. Utilizing a range of animal models and studies in the human itself, we now have a remarkable understanding of the mechanisms involved in the formation of a functional enteric neuromusculature. It is clear that development is a complex spatiotemporal process involving the coordinated interplay of a number of genes regulating cellular properties and organogenesis. This complexity is reflected in one of the most commonly recognized gut motility disorders, Hirschsprung's disease, a condition caused by a failure of development of the enteric nervous system. The ontogeny of motility patterns within the GI tract is now understood in great detail. Utilizing new technologies, animal models, and some studies in humans, researchers have been able to show that GI motility is regulated by a number of mechanisms that vary in relation to stage of development, maturity, and region within the GI tract. It is very likely that the coming years will see an increasing recognition of the developmental and related functional pathogenic mechanisms underlying a range of disorders involving enteric nerves, muscles, and interstitial cells of Cajal. The rich sensory innervation that not only underlies the normal functioning of the GI tract but has increasingly been implicated in a range of functional GI disorders is thoroughly described. This sensory innervation and its processing appear to be plastic and influenced by a number of disease mechanisms and clinical states including infection, inflammation, and psychological stress. How visceral sensation is modulated by the interplay among the CNS, neurogastrointestinal system, inflammation, and gut microbial ecosystem especially in relation to irritable bowel syndrome is addressed in a subsequent chapter. This theme is further developed with the discussion of the biopsychosocial influences on enteric neuromuscular function and how the social and cultural settings of patients act to modify physiologic responses.

The belly of the book summarizes the practical investigations that are available in the pediatric neurogastroenterologist's armamentarium. In many respects, this is where much of the recent strides of the field have taken place, moving it into the realms of a high-tech futuristic specialty. Major highlights have been the advent of impedance and high-resolution manometry technologies, which did not exist when the first textbook on pediatric gastrointestinal motility was published but are now well accepted and standardized diagnostic techniques. The role of sensitivity tests, namely, barostat and satiety drinking tests, in recognizing altered gut sensation as a key pathophysiologic component of functional gastrointestinal disorders is discussed. The application to clinical investigation of radionucleotide scintigraphy tests, which have seen in recent years a wider application given their improved tolerability, cost, and safety profile, is described in detail. Older and newer technologies ranging from electrogastrography and transit studies to 3D ultrasonography and the wireless motility capsule are presented. Finally, there is a discussion of autonomic function testing as indirect measure of gastrointestinal function. The subsequent chapters deal with the practical approach to and description of the pathology of disorders of enteric neuromusculature and the genetic underpinning of motility disorders.

The next section of the book focuses on a journey through the GI tract, detailing motility disorders that occur in each region. Feeding and swallowing disorders in a range of GI and systemic diseases are discussed. Pediatric esophageal and gastric motor disorders are summarized, and intestinal pseudo-obstruction syndrome and Hirschsprung's diseases, the most severe forms of GI dysmotility, are discussed in great detail. The book then focuses on secondary (malformative) and postsurgical motor disorders.

The book then transitions from more classic motility disorders to functional GI disorders, arguably one of the most common and challenging group of conditions encountered by primary care providers and subspecialists. The role of the Rome criteria in developing the field of pediatric functional disorders is highlighted. Infant regurgitation and gastroesophageal reflux disease, infantile colic, functional dyspepsia, irritable bowel syndrome, cyclic vomiting syndrome, aerophagia, adolescent rumination syndrome, and functional constipation are discussed.

The final section of the book is dedicated to therapy, including pharmacotherapy, cognitive behavioral therapy, gastric electrical stimulation, intestinal transplantation, and the potential use of stem cells.

Montreal, QC, Canada — Christophe Faure
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Preface

We are thrilled to be able to present the second edition of our textbook. In 2012 when we launched the first edition, we remarked on the rapid emergence of clinical pediatric neurogastroenterology and motility as a major focus within pediatrics and as a specialty in its own right. Only 4 years later did we come to realize that this transformation was occurring at an unprecedented rate (somewhat at odds with the normal rate of flow in the world of motility disorders!) and we needed to respond with a state-of-the-art revision of the textbook. This was followed by the recognition of the tremendous expertise that now exists within the field and how attractive it had become among an up and coming genre of young clinicians and researchers. The plethora of experts that we are able to garner has of course made our task easier, and we are hugely grateful to all those who have kindly agreed to devote their valuable time to have their brain power harnessed and crammed it into this second edition of the textbook.

We have tried to make the book more practical and clinically applicable yet provide the reader with an up-to-date insight into the basic science that underlies the spectrum of motility disorders.

The overall layout of the book has remained the same but we have made key changes and additions. All chapters have been updated along with an emphasis on clinical application. Chapters on investigations contain color images and have been restructured to provide a uniform overview of techniques and their practical use. New chapters have been commissioned including, among others, the introductory section on the functional interconnectivity of the enteric nervous system, the microbiome, an update on the Rome criteria, chronic intestinal pseudo-obstruction, infantile colic, imperforate anus, rumination syndrome, constipation, electrical stimulation/pacing, and drugs affecting the brain.

We are pleased that this book has become the reference textbook for pediatric neurogastroenterology and motility and trust that both specialists and generalists will continue to find this invaluable. Happy reading!

Montreal, QC, Canada — Christophe Faure
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Part I

Physiology and Development of Enteric Neuromuscular System and Gastrointestinal Motility

Introduction to Gut Motility and Sensitivity

1

Christophe Faure, Nikhil Thapar, and Carlo Di Lorenzo

Evolution, the Gastrointestinal Tract, and the "First Brain"?

Whether or not one believes in the theory of evolution, it is apparent that some of the first multicellular organisms to have inhabited the earth, including the presumptive earliest ancestors of humans, were elongated structures with a core gut tube [1, 2]. In the absence of an obvious heart, brain, or liver, this core system helped sustain life by performing fundamental processes including respiration, the assimilation of nutrition, and metabolism. On this basis it is perhaps not surprising that the gastrointestinal (GI) tract has evolved to become one of the most complex and diverse organs of the human body, with an incredible repertoire of activities from digestion, absorption, and excretion to homeostatic, endocrine, and immune functions. Many of these processes are dependent on highly coordinated sensory and effector mechanisms, which monitor the GI lumen and wall and respond to specific cues. In conjunction with a drive to maintain homeostasis within the body, the effector mechanisms regulate blood flow, adjust the balance between absorption and secretion, and coordinate mixing and propulsion of luminal contents along the length of the bowel. This latter "motility" activity is executed by region-specific peristaltic contractions and emptying mechanisms, which are dependent on highly coordinated interactions among the components of the gut neuromusculature. These components comprise the intrinsic nervous system of the gut (enteric nervous system—ENS), the smooth muscle coats, and the interstitial cells of Cajal (Fig. 1.1).

It is the mere presence and complex characteristics of the ENS that also lends itself to the notion of the gastrointestinal tract as a pioneer organ, with the potential emergence of the ENS prior to that of a recognizable brain. Therefore, perhaps, the ENS should be referred to as the "first brain," with the argument that the central nervous system (CNS) evolved subsequently, as organisms acquired locomotion and more complex interactions with the environment. Either way, perhaps reflective of a common development, the ENS shares many similarities with the CNS, including an overall inherent complexity in structure, organization, and function. It contains as many neurons as the spinal cord and a diversity of neuronal subtypes and properties of enteric glial cells akin to that seen in the CNS [3, 4]. Perhaps even more importantly, the brain and ENS appear to be functionally hardwired reflected in an almost complete interrelation between stress or psychological factors and gut function. Many of the functional gastrointestinal disorders discussed within this book appear to have a clear basis in complex interactions between biological, psychological, and social factors. Equally, nonfunctional or organic conditions have significant impacts on psychosocial well-being. This interplay has made neurogastroenterology and motility one of the most interesting but challenging fields requiring a multidisciplinary approach.

The Enteric Nervous System

The enteric nervous system (ENS) represents the intrinsic nervous system of the GI tract and is present along its entire length. The ENS is one of the largest and more complex components of the peripheral nervous system and organized as plexuses of interconnected ganglia that enmesh the GI tract. In the small and large intestine, these plexuses are present in two distinct layers, the outer myenteric plexus that sits between the inner circular and outer longitudinal muscle layers and the inner sub-

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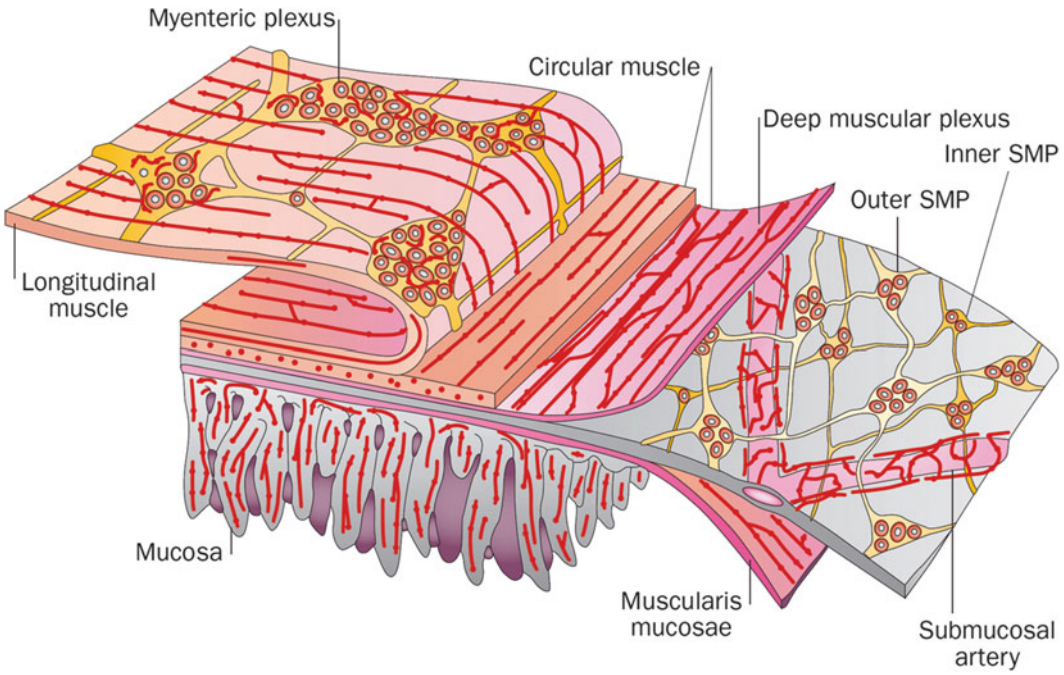

Fig. 1.1 The organization of the ENS of human and medium–large mammals. The ENS has ganglionated plexuses, the myenteric plexus between the longitudinal and circular layers of the external musculature, and the SMP that has outer and inner components. Nerve fiber bundles connect the ganglia and also form plexuses that innervate the longitudinal muscle, circular muscle, muscularis mucosae, intrinsic arteries, and the mucosa. Innervation of gastroenteropancreatic endocrine cells and gut-associated lymphoid tissue is also present, which is not illustrated here. *Abbreviations*: *ENS* enteric nervous system, *SMP* submucosal plexus (From Furness JB. The enteric nervous system and neurogastroenterology. Nat Rev Gastroenterol Hepatol. 2012;9(5):286–94. Reprinted with permission from Nature Publishing Group)

mucosal plexus present between the mucosa and the inner circular muscle layer. The ENS comprises neurons and glia organized into aggregates of cell bodies or ganglia. These are interconnected by bundles of nerve fibers that run along the individual plexuses as well as those that run between them. The real complexity of the ENS is revealed at the ultrastructural level where an intricate circuitry is evident (Fig. 1.2). A variety of neuronal subtypes partakes in this and can be classed in terms of functional and structural characteristics. Subclasses include sensory and motor, excitatory, and inhibitory. There are other neuronal subtypes and neurotransmitters present within the ENS (Table 1.1) akin to and aligned with those present in the CNS befitting the title conferred upon the ENS as the "second brain."

The development of the ENS is similarly complex (Chap. 2). The neurons and glia of the ENS all arise from precursor cells derived from the vagal, sacral, and rostral trunk neural crest [5, 6]. These cells migrate into the oral and anal ends of the embryo and enter the foregut and hindgut [7], colonizing the entire gastrointestinal tract. ENS maturity results from an adequate number of correctly differentiated neurons with sufficient axon outgrowth and branching. Several lines of evidence show that enteric neuronal development is not completed at birth. Indeed, in the murine gut, changes in morphology of the plexuses [8] and in the total number of neurons have been reported between the first 4 weeks of life [9]. Submucosal plexuses appear later than myenteric plexuses, and the number of submucosal neurons also increases during the same time period [10]. New postmitotic neurons continue to appear until 3 weeks of postnatal life in the rat gut [11]. Although the pan neuronal marker PGP9.5 is present very early in the embryonic gut (E10.5 in the mouse) [12, 13], neurochemical phenotypic differentiation occurs later during embryonic development and even in postnatal life for cholinergic and peptidergic neurons [14, 15]. ENS neurochemical maturation reaches an adult pattern only at 1 month of postnatal life. In infants, data on functional maturation of the ENS are lacking but it has been reported that the number of cell bodies present within ganglia appears to change according to the age of the individual between 1 day of age and 15 years [16].

Enteric Muscle Coats

The smooth muscle of the gastrointestinal tract, although present within the mucosa and the blood vessels of the submucosa, is primarily organized into three discrete muscle layers. The innermost, muscularis mucosa, sitting between the mucosa and submucosa, is the least developed of these layers, being only a few cells in thickness. The other two, grouped

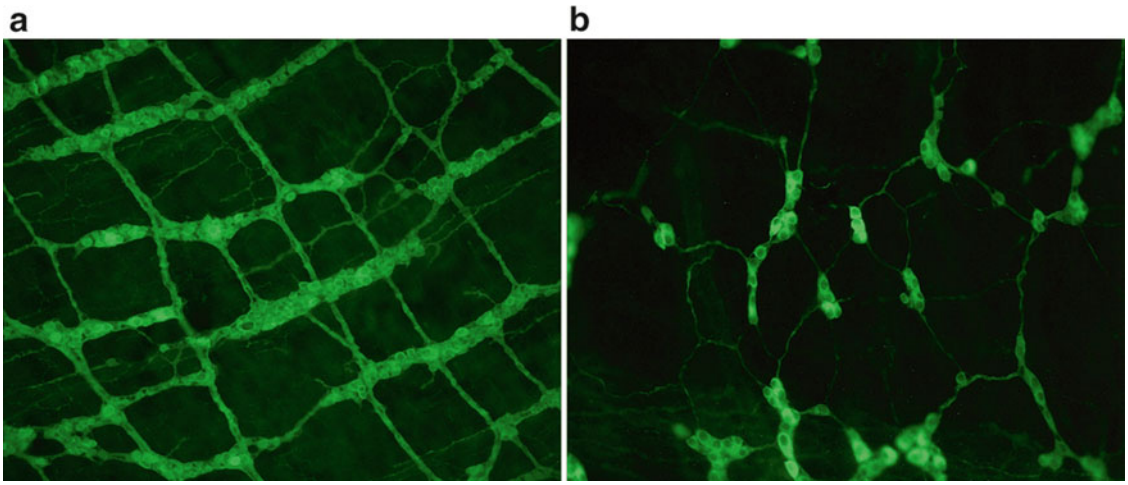

Fig. 1.2 Whole mount preparation of rat myenteric (**a**) and submucosal (**b**) plexuses (immunofluorescent staining with an antibody to the neuronal marker PGP9.5). Neuronal cells are grouped together in ganglia that interconnect both within and between the myenteric and submucosal plexuses. The neuronal cells of the plexuses comprise the enteric nervous system, and along with the glial cells, smooth muscle cells and interstitial cells of Cajal are the intrinsic components of the enteric neuromusculature

Table 1.1 Multiple transmitters of neurons that control digestive function

Type of neuron	Primary transmitter	Secondary transmitters, modulators	Other neurochemical markers
Enteric excitatory muscle motor neuron	ACh	Tachykinin, enkephalin (presynaptic inhibition)	Calretinin, γ-aminobutyric acid
Enteric inhibitory muscle motor neuron	Nitric oxide	VIP, ATP, or ATP-like compound, carbon monoxide	PACAP, opioids
Ascending interneuron	ACh	Tachykinin, ATP	Calretinin, enkephalin
ChAT, NOS descending interneuron	ATP, ACh	ND	Nitric oxide, VIP
ChAT, 5-HT descending interneuron	ACh	5-HT, ATP	ND
ChAT, somatostatin descending interneuron	ACh	ND	Somatostatin
Intrinsic sensory neuron	ACh, CGRP, tachykinin	ND	Calbindin, calretinin, IB4 binding
Interneurons supplying secretomotor neuron	ACh	ATP, 5-HT	ND
Noncholinergic secretomotor neuron	VIP	PACAP	NPY (in most species)
Cholinergic secretomotor neuron	ACh	ND	Calretinin
Motor neuron to gastrin cells	GRP, ACh	ND	NPY
Motor neurons to parietal cells	ACh	Potentially VIP	ND
Sympathetic neurons, motility inhibiting	Noradrenaline	ND	NPY in some species
Sympathetic neurons, secretion inhibiting	Noradrenaline	Somatostatin (in guinea pig)	ND
Sympathetic neurons, vasoconstrictor	Noradrenaline, ATP	Potentially NPY	NPY
Intestinofugal neurons to sympathetic ganglia	ACh	VIP	Opioid peptides, CCK, GRP

5-HT 5-hydroxytryptamine, *Ach* acetylcholine, *CCK* cholecystokinin, *ChAT* choline acetyltransferase, *CGRP* calcitonin gene-related peptide, *GRP* gastrin-releasing peptide, *ND* not determined, *NPY* neuropeptide Y, *NOS* nitric oxide synthase, *PACAP* pituitary adenylate cyclase-activating polypeptide, *VIP* vasoactive intestinal peptide

Adapted from Furness JB. The enteric nervous system and Neurogastroenterology. Nat Rev Gastroenterol Hepatol. 2012;9(5):286–94. Reprinted with permission from Nature Publishing Group

within the muscularis propria, are much thicker and comprise the inner circular muscle layer, with its cells arranged concentrically, placed between the submucosa and the myenteric plexus of the ENS, and the outer longitudinal muscle layer, with its cells running along the long axis of the gut, placed between the myenteric plexus and the outermost serosal layer. In the small intestine, the circular muscle appears well developed in sequential segments along its length giving the appearance of concentric rings. In the large intestine, bands of smooth muscle and connective tissue (taenia coli) run on its outside along its length. Their functional role is not completely clear. The enteric smooth muscle is organized in syncytia of cells that are electrically coupled to elicit upon activation contractile activity of the muscle layers. The circular and longitudinal muscles work in concert by contracting to result in segmentation and shortening to execute peristalsis and aboral propulsion of gastrointestinal luminal contents. Contraction of smooth muscle cells derives from two basic patterns of electrical activity across the membranes of smooth muscle cells: slow waves and spike potentials. The membrane potential of smooth muscle cells fluctuates spontaneously. These fluctuations spread to adjacent cells, resulting in "slow waves" which are waves of partial depolarization. The frequency of slow waves varies according to the localization in the GI tract: in the stomach, they occur at a frequency of 3 per min, in the duodenum jejunum 12–15 per min, and in the ileum 8 per min. Slow-wave activity is an intrinsic property of smooth muscle cells independent of intrinsic innervation. "Spike potentials" which result from exposition to excitatory transmitters occur at the crest of the slow waves and provoke muscle contractions at a maximal rhythm dependent upon slow-wave frequency.

Interstitial Cells of Cajal

In 1893, a Spanish physician and professor of pathology provided the first description of a distinct group of cells that appeared to reside in the "interstitium" between enteric nerves and smooth muscles. These cells, now termed interstitial cells of Cajal (ICC), are now established as critical components of the enteric neuromusculature regulating gastrointestinal motility, playing roles as pacemakers and as mediators of enteric motor neurotransmission. They are present in a number of subtypes and morphologies throughout the layers of the GI tract, each of which may relate to distinct physiological functions. One of the key ICC subtypes, ICC-MY, is present in highly branching networks within the myenteric plexus of the small intestine and appears to initiate slow waves that are spread passively to the adjacent electrically coupled smooth muscle cells. Depolarization of neighboring smooth muscle cells leads to activation of the contractile apparatus. There has been considerable recent interest in the potential role of ICC disorders in the pathogenesis of human gut motility disorders (reviewed by Burns [17]), and loss and reduced ICC numbers have been implicated in Hirschsprung's disease, slow transit constipation, chronic intestinal pseudo-obstruction, and esophageal achalasia. Some debate exists over whether there is true loss of ICCs, dedifferentiation, or loss of the cell surface receptor that defines ICCs c-kit. ICCs appear capable of transdifferentiation to smooth muscle cells, a cell type with which they share the same mesenchymal progenitor. Regeneration of ICCs also appears possible [18]. Further studies are required to understand the role of ICCs in disease.

Control of the Enteric Neuromusculature and the Gut-Brain-Microbiota Axis

Although it has been recognized that the neuromusculature of the gut is capable of independent function, this largely relates to fairly rudimentary observations of the retention of basic functions such as contractility, which depend on the integrity of intrinsic reflex circuits that integrate sensory inputs and effector outputs, both excitatory and inhibitory. Thus, in the experimental setting, segments of isolated gut dissected out of the body and placed in a water bath in vitro are capable of efficiently propagating a bead introduced at its rostral end. However, as discussed above, it has long been recognized that the gastrointestinal tract is a portal for, and dependent on, a whole multitude of interactions that facilitate its many and varied functions.

In addition to the complex interactions with the CNS, it is clear that the autonomic nervous system (ANS) exerts critical control of gastrointestinal function. Like the ENS, the ANS is also part of the peripheral nervous system and traditionally further subdivided into the parasympathetic and sympathetic nervous systems with craniosacral and thoracolumbar outflows, respectively. Much of the parasympathetic innervation to the GI tract travels via the vagus nerve and sacral nerves and the sympathetic along mesenteric blood vessels from the prevertebral ganglia. These tracts carry both sensory and motor innervation. Akin to their other functions, these two subdivisions schematically function in opposition to each other with the parasympathetic primarily excitatory to gut function by promoting secretion and peristalsis and mainly mediating physiological (nature and composition of the intestinal content and motility and contractile tension of the smooth muscle) rather than harmful sensations and the sympathetic inhibitory by decreasing peristalsis and reducing perfusion of the GI tract and transmitting information on potentially noxious stimuli. As a consequence, disorders of the autonomic nervous system are related to disturbances in GI motility and sensing.

Beyond control by the CNS and ANS, the extrinsic modulation of the ENS is much more complex. This is reflected in the multiplicity of factors involved in its development

from connective tissue and through to functional interaction with other organ systems such as the immune and endocrine systems. In children, this process is further complicated by ongoing growth, development, and maturation of the gut and its immune system as well as their interaction and adaptation to postnatal life including psychosocial influences, environmental and dietary factors, as well as establishment and changes in the microbiome. This concept of integrated activity across biological and psychosocial systems is one of the most fundamental that has arisen in the field of neurogastroenterology and reflected in the recognition and study of what is now referred to as the gut-brain-microbiota axis, which also incorporates the neuro-immune interactions that occur within the gut itself (Chaps. 4 and 5) [19]. Using the example of childhood functional abdominal pain disorders, Fig. 1.3 illustrates the putative role of the bio-psycho-social model and gut-brain-microbiota axis in the pathogenesis of disease.

Not only does disruption of these factors and their interactions contribute to symptoms, its integrated working

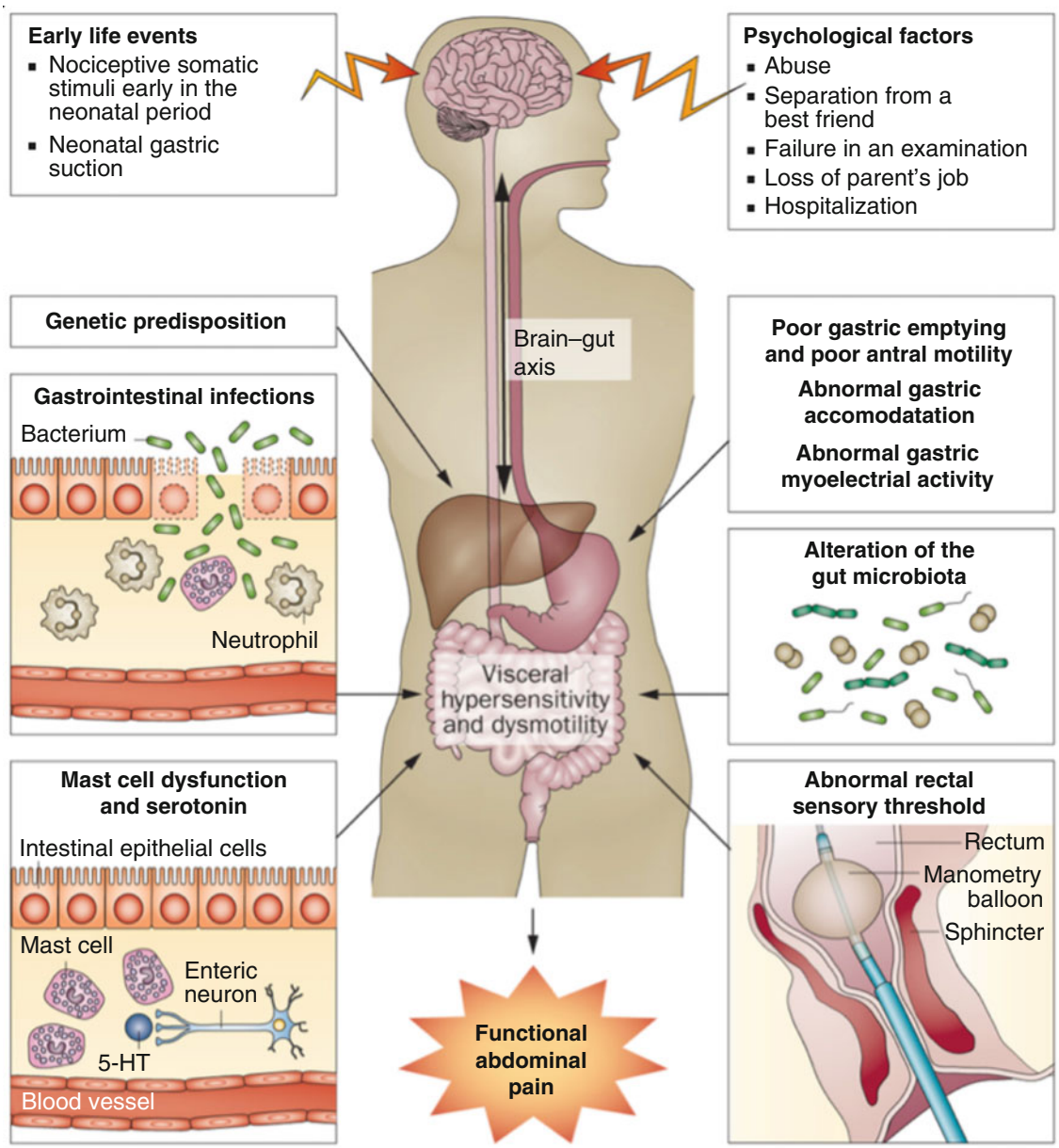

Fig. 1.3 Pathogenesis of childhood functional abdominal pain. Several risk factors are associated with changes in visceral hypersensitivity and motility and contribute to the development of functional abdominal pain. *Abbreviations*: *5-HT* 5-hydroxytryptamine, *FGID* functional gastrointestinal disorder (From Korterink J, Devanarayana NM, Rajindrajith S, et al. Childhood functional abdominal pain: mechanisms and management. *Nature Reviews Gastroenterology & Hepatology,* **12**, 159–171, 2015. Reprinted by permission from Macmillan Publishers Ltd.)

appears susceptible to being "programmed" especially at an early age to give rise to pathology later on in life. Of these, recurrent abdominal pain (Chaps. 36 through 38) appears to provide a key paradigm for such "programming" (Fig. 1.3). It follows, therefore, that there are an enormous range of potential etiopathogenic factors acting over a considerable time period of development that could result in gut motility disorders. This functionality is of course affected by noxious and genetic influences occurring during development that determine the structural and functional viability of its components.

Sensory Function and the Gastrointestinal Tract

Gut motility disorders are often seen as synonymous with dysfunction of motor activity of the GI tract. Certainly, the most severe disorders are predominated by disturbances or failure in propagation of luminal contents. It is clear, however, that sensory functions of the GI tract are similarly important and dysfunction often carries significant bearing on the ultimate impact of disease. Although particularly evident in functional GI disorders, sensory symptoms are present throughout the spectrum of GI motility disorders (Chap. 4).

Normally, most of the information originating from the GI tract does not reach the level of conscious perception and is processed in the brainstem. Other sensations such as hunger, fullness, satiety, bloating, and need to defecate that involve adapted behaviors do reach the cortex. As previously stated, extrinsic innervation of the GI tract is composed of vagal, spinal visceral (sympathetic), and sacral nerves. These nerves contain afferent (or sensory) fibers that transmit information from the viscera to the CNS and efferent fibers that transmit information from the CNS to the gut. At the level of the gastrointestinal tract, sensory neurons and entero-endocrine cells serve as transducers. The central processing of visceral sensitivity is complex and involves the somatosensory cortex which provides information about intensity and localization of the stimulus, the anterior cingulate cortex which mainly processes pain characteristics and cognitive aspects of the pain experience, the insula which integrates internal state of the organism, and the prefrontal cortex which is believed to play a key role in the integration of sensory information and in the affective aspect of the sensation. Therefore, it appears that, similar to motor disorders, visceral sensory disorders may result from multiple factors and are prone to be influenced by complex interactions with cognitive and behavioral components [20].

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Development of the Enteric Neuromuscular System

2

Tiffany A. Heanue and Alan J. Burns

Gut Embryogenesis

The gut begins to form around the 14th day after fertilisation in the human as an endoderm-derived primitive tube that subsequently becomes surrounded by splanchnic mesoderm. Of the three germ layers, the endoderm gives rise to the epithelial lining and glands, such as the liver and pancreas, of most of the gut, the ectoderm gives rise to the oral cavity (proximal stomatodaeum) and the anus (distal proctodaeum), and the mesoderm-derived splanchnic mesenchyme gives rise to the smooth muscle and connective tissue. As development proceeds and the gut lengthens, it differentiates into three regions: foregut, midgut and hindgut. The foregut subsequently develops into the pharynx, oesophagus, stomach and the proximal portion of the duodenum down to the opening of the bile duct, as well as the liver, biliary system and pancreas. The midgut gives rise to the remainder of the duodenum, the small intestine and portions of the large intestine including the caecum, appendix and colon to the distal transverse colon. The hindgut develops into the distal part of the transverse colon, the descending colon, the rectum and the proximal part of the anal canal. The blood supply to the foregut, midgut and hindgut comes from the coeliac artery, the superior mesenteric artery and the inferior mesenteric artery, respectively.

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Smooth Muscle Development

Stages of Smooth Muscle Development

The smooth muscle of the gut derives from the splanchnic layer of the lateral plate mesoderm, which is recruited to the primitive gut tube by signals derived from the endoderm and is induced to proliferate and undergo gut-specific mesoderm differentiation (reviewed in [1]). Sonic hedgehog (Shh) is a key signalling molecule in early endoderm-mesoderm interactions. Shh is part of the hedgehog (Hh) family of cell signals known to be involved in crucial developmental processes in both invertebrate and vertebrate species. *Shh* is expressed in the endoderm of the gut, and the receptor for Hh, *Patched-1 (Ptc-1),* is highly expressed in the adjacent mesoderm (reviewed in [2]). *Shh−/−* mice have significant gut defects that include a reduction in smooth muscle [3]. Gli family members (*Gli1*, *Gli2*, *Gli3*), which are all transcription factors mediating the Hh pathway, have also been shown to be involved in gut development. Thus Hh signalling is essential for GI tract organogenesis, and considerable evidence suggests that defects in this pathway are involved in a number of human gut malformations including intestinal transformation of the stomach, duodenal stenosis, reduced smooth muscle, abnormal innervation of the gut and imperforate anus [3].

Within the embryonic gut, smooth muscle precursors are initially small and round in shape, but as differentiation proceeds, cells become elongated, circumferentially arranged and parallel to one another and will form the circular muscle layer [4]. Cells from the outer portion of the circular layer stretch radially outward, towards the presumptive longitudinal layer, and then form bundles and bend perpendicularly to form an L shape, thus acquiring the correct orientation of the longitudinal muscle layer [4]. The last layer of smooth muscle to form at the base of the mucosal villi, the muscularis mucosa, also forms during embryogenesis [4]. This radial patterning of the gut muscle occurs similarly along the length

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of the gastrointestinal tract, though exhibiting a rostral-to-caudal gradient of maturation, and takes place well before birth [5–7]. In the human gut, the longitudinal, circular and muscularis mucosae layers of smooth muscle are evident by week 14 of development [7] (Fig. 2.1). The massive (1000-fold) increase in amount of the smooth muscle of the gut from embryogenesis to adult stages is accomplished by a combination of a three- to fivefold increase in cell size and a 200–300-fold increase in cell number through mitotic division of existing muscle cells [5].

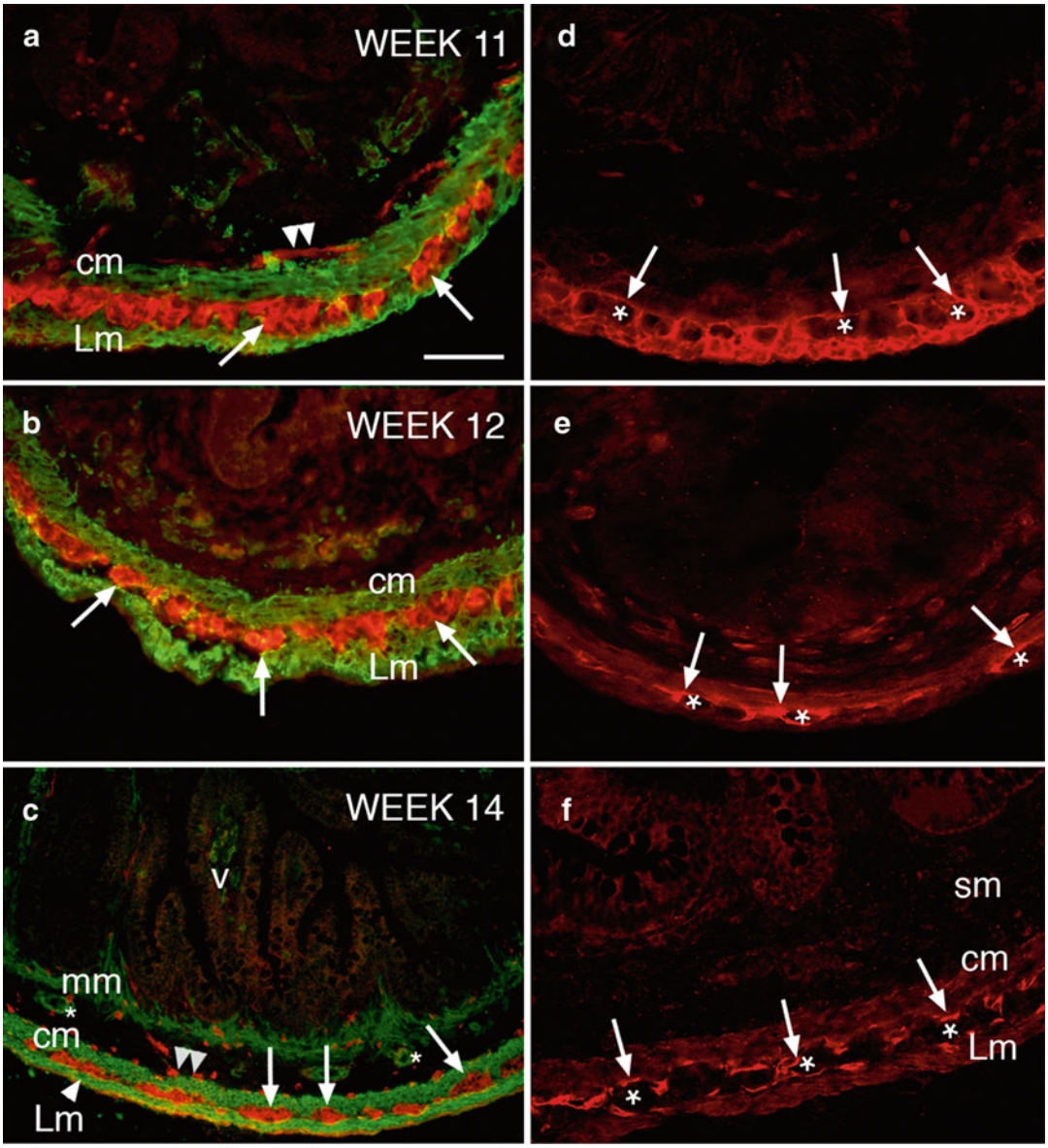

Fig. 2.1 Development of enteric nervous system, smooth muscle and interstitial cells of Cajal within the developing human gut. (**a**) At week 11 of development, αSMA-staining (*green*) is apparent in the circular (cm) and longitudinal (Lm) muscle layers, located on either side of the $p75^{NTR}$-positive (*red*) cells (the neural crest-derived cells, *arrows*) of the presumptive myenteric plexus. Occasional areas of $p75^{NTR}$ immunoreactivity are also apparent in the region internal to the circular muscle layer, corresponding to the presumptive submucosal plexus (*double arrowheads*). (**b**) At week 12, the circular (cm) and longitudinal (Lm) muscle layers are strongly immunopositive for αSMA. Between the muscle layers, $p75^{NTR}$ labelling is present in groups of cells comprising myenteric ganglia (*arrows*). (**c**) At week 14, αSMA labelling is strong in the circular (cm) and longitudinal (*arrowhead*, Lm) muscle layers and weak in the muscularis mucosae (mm), adjacent to the villi (v). The walls of blood vessels within the submucosa are also immunopositive for αSMA (*asterisks*). $p75^{NTR}$ staining is present within ganglia of the myenteric plexus (*arrows*) and in nerve fibres within the submucosa (*double arrowheads*). (**d**) At week 11, Kit immunostaining is widespread within the developing smooth muscle layers, particularly surrounding (*arrows*) the presumptive myenteric ganglia (*asterisks*). At week 12 (e) and week 14 (f), Kit-positive ICC (*arrows*) is restricted to the areas surrounding ganglia (*asterisks*). Scale bar = 50 μm (**a**, **b**); 100 μm (**c**). (From Wallace, A.S. and Burns, A.J. (2005) Development of the enteric nervous system, smooth muscle and interstitial cells of Cajal in the human gastrointestinal tract. Cell and Tissue Research: 319, 367–382 (modified from Figures 7 and 8, with kind permission of Springer Science + Business Media))

Peristaltic function of the gut requires the development of the contractile apparatus of the smooth muscle cells, which enables the cell to tense and relax, thus generating the contractile motion. The contractile apparatus is comprised of bundles of actin and myosin filaments (myofilaments), attached to the cell membrane via actin-rich dense bodies (the functional equivalent of Z lines in skeletal muscle). Upon receipt of contractile stimulus and signal activation, the myosin (thick) filaments slide over the actin (thin) filaments to produce cellular contractions [8]. Myofilaments are oriented in parallel arrays along the long axis of the smooth muscle cells and cause shortening along this axis. Studies of chick embryonic intestine demonstrate that upon aggregation and elongation of muscle precursors, the first indications of the developing contractile apparatus are evident as thin bundles of actin filaments, which are initially unattached to the cell membrane [5]. Several days later, thick myosin filaments form, which are also unattached to the cell membrane. Soon after birth, however, extensive insertion of the contractile apparatus to the cell membrane is evident, with abundant microtubules oriented parallel to the cell length [5].

Although smooth muscle can undergo spontaneous contractions, coordination of these contractions is regulated through intrinsic innervation by nerves of the ENS (see below). Because smooth muscle cells of the gut are uninuclear, in contrast to multinuclear skeletal muscle cells, neighbouring smooth muscle cells communicate via gap junctions to enable passage of electrical impulses between cells and to allow generation of the coordinated progressive wave contractions characteristic of the gut wall. These gap junctions are observed perinatally in intestinal smooth muscle [5] consistent with the neuronally mediated organised peristaltic activity that commences just before feeding begins at birth [9]. However, ENS- and ICC-independent organised spontaneous contractions can also be observed in mouse intestine several days before birth [10]. Because gap junctions are not observed at these earlier time points, the mechanisms enabling such organised smooth muscle contractions are currently unknown.

Smooth Muscle Development Defects in Motility Disorders

Hirschsprung's disease (HSCR) is a common developmental disorder characterised by the absence of enteric neurons and glial cells in a variable portion of the distal gut [11–14]. In the aganglionic region of the affected gut, the smooth muscle is tonically or spastically contracted, which leads to bowel obstruction. Why an absence of ENS neurons would lead to such muscle contraction is currently unclear. One hypothesis is that this results from the absence of innervation by fibres from relaxant neurons [15, 16], while an alternative model is that over-proliferation of extrinsic, stimulatory nerve fibres leads to increased contractility of affected segments [17]. Further experimentation will be necessary to distinguish between these and other models and to shed light on why smooth muscle remains contracted in affected segments in HSCR.

Interestingly, in certain mouse models of HSCR, aganglionic segments exhibit an increased thickness of the circular and longitudinal muscle layers [18], and these thicker muscle regions display an increased contractile force [19, 20]. However, defects in muscle layers are not observed in all models of aganglionosis [21, 22]. Thus, muscle hypertrophy may not provide a generally applicable explanation for tonic contraction of affected segments in HSCR or other motility disorders, although it may provide explanation for disease features in some cases.

Defects in smooth muscle characterise some rare cases of chronic intestinal pseudo-obstruction (CIPO), and these are classified as myopathic CIPO and, like most cases of CIPO, are largely idiopathic [23]. Mouse mutations affecting the development of gut smooth muscle have been identified and include defects in the proliferation of smooth muscle progenitors and radial patterning of the gut [24]. Further studies in mouse or other model organisms are helping to uncover the basic cellular processes required for normal development of smooth muscle and therefore shed light on the genesis of human gut diseases.

The Enteric Nervous System

The smooth muscle of the gut is innervated by intrinsic neurons of the enteric nervous system (ENS). In addition, extrinsic nerves, comprising vagal and spinal afferent neurons that have their cell bodies outside the gut and communicate to the CNS, make axonal connections to ENS neurons and modify their activity [25–28]. Here we focus on the gut intrinsic ENS, which can function independently of the CNS to maintain local reflex activity to control muscular mixing and peristaltic movements, changes in blood flow and secretion of water and electrolytes [25].

The ENS consists of interconnected ganglia, containing neurons and glial cells. Ganglia are organised in two plexus layers which span the length of the gut, an outer myenteric plexus, situated between the longitudinal and circular muscle layers, and an inner submucosal plexus lying between the circular muscle and the muscularis mucosae [25]. ENS neurons function to innervate appropriate target tissues, such as the muscle, the mucosa and the blood vessels of the gut and to create interconnections to other ENS neurons and ganglia as well as to extrinsic neurons. Such a wide spectrum of functional requirements is satisfied by vast numbers (millions of neurons in the small intestine [29]) of different neu-

ronal types [30]. Overall the ENS is estimated to contain more neurons than found in the spinal cord [31]. ENS glial cells are even more numerous (fourfold) than neurons and function as support cells for ENS neurons and may also play a role in modulating neuronal activity or in interactions with other gut cell types such as endothelial cells and intestinal epithelial cells [32]. Following injury, glial cells also can give rise to new neurons [33]. Recently, the diversity of enteric glial cells (EGCs) has been described and includes four morphologically distinct populations that occupy unique niches within the gut and that have distinguishable physiological properties [34]. Moreover, one of these subpopulations, EGCs in the lamina propria of the mucosa, has been shown to be responsive to microbiota in the gut lumen and is replenished as necessary by glial cells that migrate from the underlying plexi [35].

Migration of ENS Precursors

The ENS derives from neural crest cells (NCC) that delaminate from the neural tube and migrate towards the developing gut tube. The primary contribution to the ENS comes from vagal NCC, which begin migration at E9.0–9.5 in the mouse, and by 4 weeks gestation in human, and enter the foregut and move in a rostral-to-caudal direction to colonise the entire gut tube by E15 in mouse and by 7 weeks gestation in human [7, 36, 37] (Fig. 2.1). In addition, trunk neural crest from the posterior vagal region makes a small contribution to the foregut ENS [37], whereas the hindgut receives contribution from the sacral neural crest, which begins their migration at a later stage, exhibits distinct migratory properties and enters and colonises exclusively the hindgut [38–41]. The myenteric ganglia emerge first during development, whereas the submucosal plexus originates later when cells from the myenteric plexus migrate through the circular muscle towards the submucosa [42] and are clearly seen in the submucosal region of the human intestine at 11 weeks of gestation [7] (Fig. 2.1).

A variety of studies have examined the behaviour and pattern of migratory enteric neural crest-derived cells (ENCCs) as they move into and along the developing gut. Time-lapse movies of fluorescently labelled ENCCs, which are rendered fluorescent through dye-labelling of cells or use of transgenic mice possessing fluorescent ENCCs, have enabled their migratory behaviours to be monitored. ENCCs are found to advance through the gut steadily as multicellular strands, with a few isolated cells preceding the migratory wavefront [43–45]. The pattern of advance changes as ENCCs reach the caecum, when the advancing strand pauses and cells separate and adopt a solitary meandering behaviour [44]. After several hours, the cells leave the caecum and continue movement through the hindgut as a network of interconnected cells to complete gut colonisation [43]**.** More recently, the importance of ENCCs that migrate from the midgut to the hindgut across the mesentery has been uncovered, and such 'trans-mesenteric' ENCCs have been shown to form a substantial portion of the hindgut ENS in mouse [46]. Finally, using new technologies to label individual ENCCs in living tissue, the trajectories of single cells have been described, revealing that a balance of non-directional and directional movements of individual cells modulates caudal advance of the population and helps to supply a uniform density of ENCCs to the gut [47]. Interestingly, immature neurons that are being generated even as ENCCs are migrating through the gut (see below) also exhibit rostral-to-caudal migration, albeit more slowly than their ENCC precursors [48]. Approximately half of the immature neurons migrate by caudal movement of cell bodies along long leading processes [48].

Among the signals involved in directing migration of NCC along the gut, perhaps the best understood are the components of the RET pathway [49]. Loss of RET signalling results in gut aganglionosis in mice [50], and the *RET* gene is the main gene implicated in HSCR in humans [11, 51, 52]. Within the gut, the RET receptor and the glycosylphosphatidylinositol (GPI)-linked GDNF family receptor α1 (GFRα1) co-receptor are expressed on NCC, and the ligand, glial cell line-derived neurotrophic factor (GDNF), is expressed within the gut mesenchyme (Fig. 2.2) and has been shown, in vitro, to be a chemoattractant for NCC [53]. Consistent with this in vitro finding, GDNF is expressed in the stomach when the ENCC wavefront is in the oesophagus and is elevated in the caecum as ENCCs migrate towards this distal part of the gut. Thus it appears that NCC move towards centres of GDNF expression that are upregulated progressively further along the gut. In addition, GDNF expression is observed in a gradient across the mesentery and is proposed to guide the trans-mesenteric ENCC migration of cells colonising the hindgut [46]. More extensive information concerning the molecular mechanisms involved in ENS development can be found in the following reviews [12, 54–58].

Proliferation in the ENS

The colonisation of the entire gut takes place over many days (E9.0 to E15 in the mouse) and from week 4 to 7 in human gestation [7], and during this period, the gut is growing considerably in length and continues to grow during further embryonic and postnatal stages. In order to continue expansion into caudal gut regions as well as to keep pace with the expanding length of the already colonised gut regions, the relatively small number of ENCCs must therefore increase greatly in number throughout the gut. For that reason, it is not surprising that proliferation of ENCCs is observed and is essentially equivalent at all rostral-caudal positions [59]. Nevertheless, the size of the starting pool of ENS progenitors

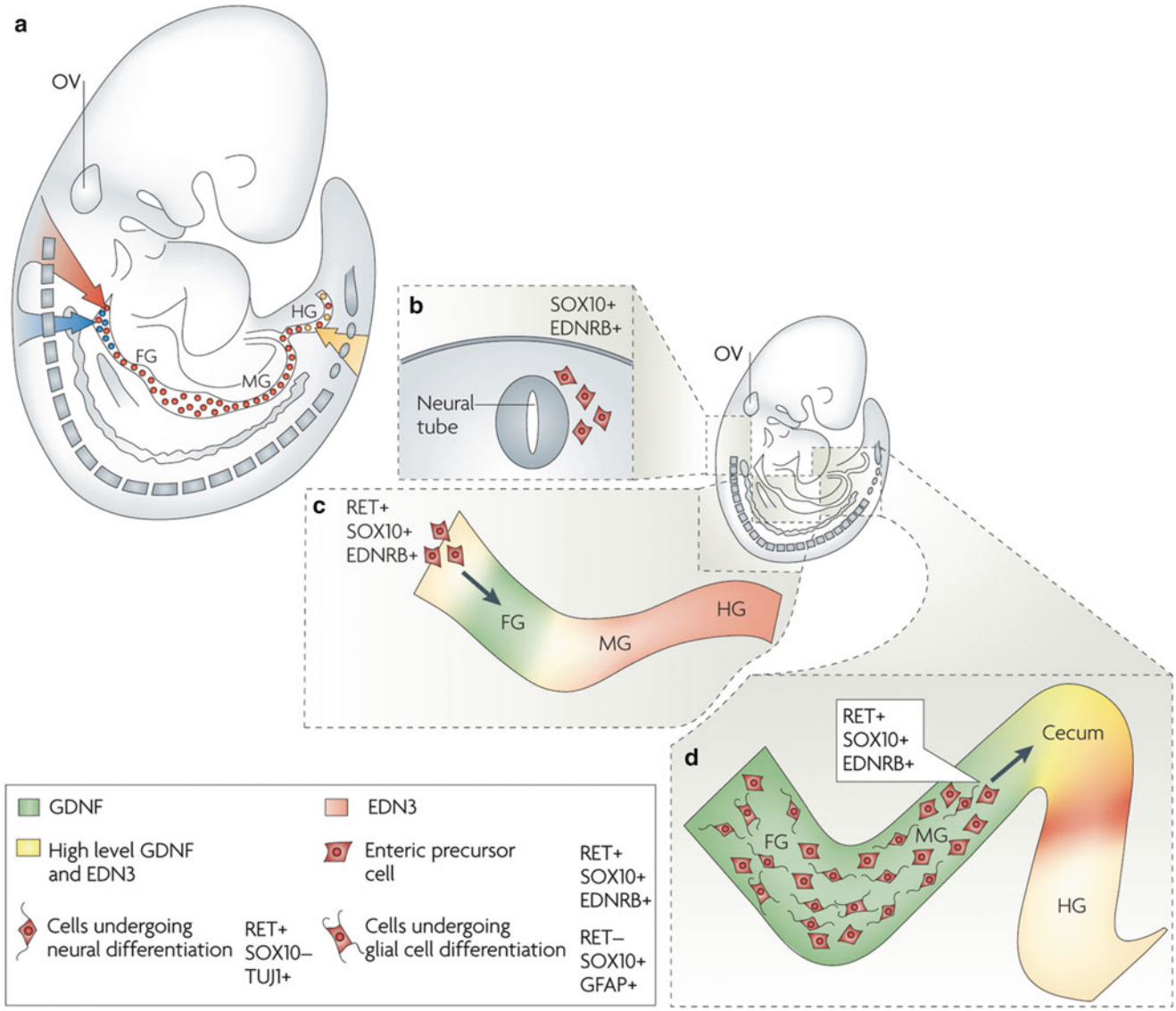

Fig. 2.2 Sources, migratory routes and gene expression in neural crest cells contributing to the ENS. (**a**) At approximately embryonic day (E) 8.5–9 in the mouse, vagal neural crest cells (*red arrow*) invade the anterior foregut and migrate in a rostral-to-caudal direction to colonise the entire foregut (FG), midgut (MG), caecum and hindgut (HG) and give rise to the majority of the enteric nervous system (ENS, *red dots*). Colonisation is complete by E15.5. The most caudal vagal neural crest cells, emanating from a region overlapping with the most anterior trunk neural crest cells (*blue arrow*), make a small contribution to the ENS of the oesophagus and the anterior stomach (*blue dots*). Finally, sacral neural crest cells (*yellow arrow*) also make a small contribution, beginning their migration at approximately E13.5 and migrating in a caudal to rostral direction to colonise the colon (*yellow dots*). (**b**) As vagal neural crest cells (*red*) emigrate from the neural tube, they express SRY-box 10 (SOX10) and endothelin receptor-B (EDNRB). (**c**) Upon entering the foregut at E9–9.5, enteric neural crest-derived cells (ENCCs) begin to express RET. Within the gut mesenchyme, the RET ligand glial cell-line-derived neurotrophic factor (GDNF) is expressed at high levels in the stomach (*green*) and the EDNRB ligand endothelin 3 (EDN3) is expressed in the midgut and hindgut (*pink*). (**d**) As ENCCs migrate caudally at approximately E11, they encounter high levels of GDNF and EDN3 expression in the caecum (*yellow*). Cells behind the wavefront begin progressive differentiation towards neural and glial cell fates. Beginning at E11.5, GDNF and EDN3 are expressed in the distal hindgut (not shown). (From Heanue and Pachnis (2007) Enteric nervous system development and Hirschsprung's disease: advances in genetic and stem cell studies. Nat Rev Neurosci 8(6): 466–479. Panel (**a**) modified, with permission from The Company of Biologists Ltd., from Durbec et al. (1996) Development 122(1): 349–358)

has a significant impact on the capacity of ENCCs to completely colonise the gut. In a number of experimental conditions in which the initial pool of ENCCs is reduced, there is a failure of ENCC to colonise the distal gut [21, 39, 60] or to appropriately populate the entire gut with ENS neurons [61]. Moreover, mathematical models which suggest that ENCC proliferation is a key driver of colonisation have been substantiated by experimental data [62–64].

Regarding molecular mechanisms influencing ENCC proliferation, the RET ligand, GDNF, has been shown to

increase the proliferation rate and numbers of enteric neural precursors in vitro and in vivo [61, 65, 66]. An additional level of control of GDNF/RET signalling is mediated by factors such as those within the endothelin receptor-B (EDNRB) pathway. Activation of EDNRB specifically enhances the effect of RET signalling on the proliferation of uncommitted ENS progenitors [67], and the EDNRB ligand, endothelin-3 (ET-3), which directly regulates ENCC proliferation and differentiation [68], modulates the action of GDNF by inhibiting neuronal differentiation [66]. Another mediator of GDNF/RET signalling is Prokineticin-1 (Prok-1) which has been shown to maintain proliferation and differentiation of ENCCs [69]. Another factor shown to be involved in ENCC proliferation is retinoic acid (RA), which enhances proliferation of subsets of ENS precursors and increases neuronal differentiation [70], and retinaldehyde dehydrogenases, that produce RA, have been shown to be involved in ENS development and function [71].

Differentiation in the ENS

The mature ENS contains a large variety of neuronal cell types and glial cells, with neuronal types distinguishable on the basis of their morphologies, immunohistochemical profiles and electrophysiological properties [30, 72–74]. Even as ENCCs are migrating through rostral gut regions, some of these ENCCs are undergoing neuronal differentiation [45, 75–77], thus beginning the process of generating the wide range of neuronal cell types present in the mature ENS. Nevertheless, ENS progenitor cells persist among the pool of ENCCs, and differentiation of distinct neuronal types continues throughout embryonic and postnatal development [74, 78]. Differentiation of glial cells begins in the late embryonic period, around E15, and continues during the postnatal period [74, 79]. Interestingly, cells expressing early neural differentiation markers can continue to proliferate [59, 75], thus providing an additional mechanism to expand ENS cell number to populate the continuously growing gut.

In order to generate the distinct classes of ENS neurons and glial cells, there is a progression during ENCC development from bipotential ENS progenitor cells, capable of giving rise to both neurons and glial cells, to separate neural and glial progenitor cells (Fig. 2.2) and the further subdivision of neural progenitors into precursors of the distinct neuronal types. While the advancement of cells through the stages of this progressive lineage restriction can be identified using molecular markers [74] (Fig. 2.2), the factors influencing the changes in cell state are largely unknown. Indeed, only a few instances have transcription factors, such as *Mash1*, which generates some serotonergic neurons [36], or *Hand2*, which is involved in the development of vasoactive intestinal polypeptide (VIP) neurons [80] and in terminal differentiation [81] been identified. In most cases, genes affecting development of the ENS affect all lineages due to defects in the survival or proliferation of early progenitor cells (reviewed in [54]). The capacity for ENS progenitor cells to be propagated in culture has the potential in the future to complement gene deletion studies in elucidation of the factors controlling progressive ENS lineage restriction.

It has been postulated that defects in the development of specific subtypes of enteric neurons may underline certain motility disorders [30]. Although some ENS neurons of the human myenteric plexus have been characterised [82–84], the cataloguing of ENS subtypes may still be too preliminary to enable motility disorders to be analysed on this basis.

Ganglia Formation and Connectivity in the ENS

Ganglia are the functional units of the ENS. To perform their tasks, they must contain the appropriate number of neuronal subtypes and innervate appropriate targets, i.e. the muscle layers, the mucosa and the blood vessels [25]. Unfortunately, the mechanisms controlling the formation of ganglia, the generation of neuronal diversity and the processes of establishing appropriate axonal connections are not well understood. Nevertheless, some evidence suggests that during development, differential cell adhesion may play a role in ganglia organisation; neurons and non-neuronal cells in ganglia have different levels of NCAM and levels of NCAM on the surface of cells correlated with differential abilities to form cell aggregates in vitro [85]. Thus adhesion may influence both composition and organisation of ganglia. Moreover, some insights concerning ganglia formation can also be obtained from various gut motility disorders. In contrast to HSCR patients that have hindgut aganglionosis and megacolon, gut dysmotility has also been reported in patients where enteric ganglia are abnormally large in size and/or number of neurons (hyperganglionosis) or reduced in size (hypoganglionosis). Hyperganglionosis occurs either as ganglioneuromas associated with multiple endocrine neoplasia type 2B (MEN2B), a heri disorder due to M918T missense mutation in the RET gene [86], or as intestinal neuronal dysplasia (IND), a controversial, inconsistently described entity, characterised by features that include increased density of submucosal ganglia, increased numbers of ganglion cells per submucosal ganglion and/or ectopic placement of ganglia [87]. Mice with mutations in the homeobox gene *Enx* (*Hox11L1*) have been suggested as a model for IND since these animals have megacolon and increased numbers of large intestinal myenteric ganglion cells [88]. In contrast to hyperganglionosis, hypoganglionosis, another condition that is difficult to diagnose by suction biopsy, has been associated with intestinal pseudo-obstruction (reviewed in [89]). Although the molecular mechanisms causing hypoganglionosis are unclear, the smaller ganglia may

result from failure of development of neuronal subclasses [90] or from gene dosage effects since *Gdnf*+/− and *Ret*+/− mice have hypoganglionosis [91, 92].

Regarding establishment of neuronal projections within the ENS, limited data reveal that early-generated neurons that transiently exhibit tyrosine hydroxylase (TH) immunoreactivity have long leading processes that project caudally and will eventually give rise to caudally projecting neurons that innervate the circular muscle or other myenteric neurons [93]. Further, analysis of single cells at mid-gestation stages has shown that neurites in general have strong caudally biased directionality [47]. These observations led to the suggestion that the same factors that guide migration of ENCCs in a rostral-to-caudal direction are influencing the direction of axonal outgrowth of this neuronal population. However, although ENCCs often migrate along neurites, ENCCs are also observed in advance of neurites [47], suggesting that the correlation isn't prescriptive. Indeed, in mutants in which neuronal processes show abnormal directionality, ENCC migration occurs normally [94], suggesting that ENCC migration is not simply guided by neurites. Another possible explanation for the correlation between ENCC migration and neurite projection is that migrating ENCCs can influence neurite outgrowth. Yet, following transplantation of ENCCs into aneural hindgut, some neurons project orally, despite confronting anally migrating ENCCs. Interestingly, sacral NC-derived ENCCs migrate along nerve fibres of the pelvic ganglia [41], and their migration may be more strictly dependent upon association with nerve fibres [95]. Thus it is likely that the factors influencing ENCC migration and neurite outgrowth of vagal- and sacral-derived ENCCs are distinct.

In the zebrafish, a correlation has been made between the orientation of smooth muscle cells and the direction of axonal projections; as circular muscle cells begin to differentiate and elongate around the circumferential axis, ENS neurons begin to extend axons circumferentially around the gut [96]. Whether such a putative organiser role for smooth muscle cell exists similarly in other vertebrate species is currently unknown. Finally, although neurons are known to make axonal connections to target tissues and express synaptic proteins even at embryonic stages [97–99], it is unknown at what time point neurons are making functionally active synaptic connections, although the relevant electrophysiological analyses are beginning to be performed [77].

Development of Interstitial Cells of Cajal

ICC: Different Forms, Different Functions

Interstitial cells of Cajal (ICC) are small network-forming cells located within the gut muscle layers that were first described by the Spanish neuroanatomist Ramon Santiago y Cajal in the late 1800s. However, it has only been in the last two decades that great progress has been made in our understanding of the morphology and physiological roles of ICC. These advances have been primarily due to the discovery that ICC express *c-kit*, the proto-oncogene that encodes the receptor tyrosine kinase Kit, the ligand for which is stem cell factor (SCF), and that anti-Kit antibody specifically labels ICC [100]. Consequently, studies using anti-Kit antibody in gut from humans and laboratory animals have revealed a range of different ICC morphologies in different gut regions ([101]; for reviews see [102, 103]). To investigate the physiological role(s) of ICC, their development was disrupted using either injection of anti-Kit antibody into mice to block ICC formation or, genetically, using *W* mutant mice that have loss-of-function mutations in the *c-kit* gene or *steel* mutant mice that are deficient in the SCF ligand for Kit. Morphological analysis of anti-kit-injected mice, or *W* or *steel* mutants, revealed a lack of ICC within the myenteric plexus of the small intestine, and physiological studies demonstrated a lack of intestinal pacemaker activity in the same gut region [100, 104–106]. Thus these studies demonstrated that ICC associated with the myenteric plexus are necessary for pacing electrical slow wave activity and contractions within GI muscles.

In addition to the pacemaker role for ICC, a role for ICC in the mediation of neurotransmission, as originally proposed by Cajal, has seemed likely since long, thin intramuscular ICC are closely apposed to varicose nerve terminals and electrically coupled via gap junctions to neighbouring smooth muscle cells [107]. Analysis of stomach tissues from *W* mutant mice that are deficient in intramuscular ICC, but have normal patterns of enteric nerve fibres and smooth muscle cells, demonstrated a lack of nitric oxide-mediated neuroregulation of smooth muscle [107]. These, and more recent findings for other neurotransmitters, confirm that intramuscular ICC play a fundamental role in the reception and transduction of both inhibitory and excitatory enteric motor neurotransmission [108] and reviewed in [109, 110].

More recently, other classes of interstitial fibroblast-like cells, such as those expressing platelet-derived growth factor receptor α (PDGFRα), have been reported to be present in the tunica muscularis of the gut [111, 112]. These cells have also been shown to be involved in transducing inputs from enteric motor neurons, this adding to the complexity of the cell types and interactions involved in the generation of coordinated gut neuromuscular activity.

Embryological Origin of ICC

ICC are derived from the mesoderm. Lecoin et al., using quail-chick interspecies grafting to genetically label the vagal neural crest cell-derived precursors of the ENS, demonstrated that in

chimeric embryos, the ENS cells were of quail (donor) origin, whereas ICC were of chick (host) origin and therefore belonged to the gut mesenchyme lineage and were not neural crest-derived [22]. These authors also cultured aneural chick gut on the chick chorioallantoic membrane and found that ICC developed in the absence of enteric neurons, thus concluding that ICC are of mesodermal origin and develop independently from the enteric neurons with which they subsequently form anatomical and functional relations. The same year, Young et al., also using gut explants, but in this case from the mouse, demonstrated that when aganglionic segments of large intestine were explanted under the renal capsule of adult mice, ICC but not neurons developed in these explants [113], again indicating that ICC do not arise from the neural crest.

In the human gut, Kit-positive ICC have been identified as early as week 9 of development, after the colonisation of the gut by NCC and following the differentiation of the circular muscle layer. Unlike these other cell types, ICC do not appear to mature in a rostrocaudal wave, as Kit immunoreactivity is more defined in the hindgut than in the midgut at week 9. ICC rapidly mature and, by week 11, Kit immunoreactivity is restricted to cells surrounding the myenteric ganglia [7] (Fig. 2.1), in a pattern that is more organised in the midgut than in the hindgut. Similar reports of ICC surrounding myenteric ganglia have been described in the human foetal small bowel [114, 115]. ICC development in the human therefore appears to lag behind that of the ENS by at least 3 weeks and slightly behind that of smooth muscle differentiation, as evidenced by αSMA immunoreactivity. A similar developmental lag for ICC has also been reported in mouse and zebrafish embryos [116–118], as ICC form after the gut has been colonised by neural precursors and after the development of αSMA immunopositive muscle.

ICC in Human Gastrointestinal Motility Disorders

Loss of ICC, or disruption of ICC networks, has been reported in a wide range of GI diseases, including achalasia, chronic intestinal pseudo-obstruction, HSCR, inflammatory bowel diseases, slow transit constipation and others (for reviews see [102, 119–121]). However, in many cases it is difficult to determine whether defects in ICC networks are the cause of motility disorders, or whether disrupted ICC networks are a consequence of gut dysfunction. For example, in disease states, a lack of Kit-labelling could either indicate an actual loss of ICC from the gut tissues or a loss-of-Kit expression from ICC which are still present within the gut but that may have a different phenotype. Experimental findings support the idea that ICC can change phenotype (or loose Kit expression) under certain conditions or insult. For example, in studies where Kit receptors were blocked during development, ICC almost entirely disappeared from the small intestine. However, closer examination revealed that ICC had not undergone apoptosis, but had developed ultrastructural features similar to smooth muscle cells. These findings highlight plasticity between ICC and smooth muscle cells that is regulated by Kit signalling [122, 123]. In addition to transdifferentiation, ICC appear to have some capacity for regeneration. In experiments where the mouse intestine was exposed to a chemical insult which induced loss of the myenteric plexus associated ICC, a few weeks later, cells with ICC-like features began to reappear [124, 125]. A further example of the difficulty in interpreting potential loss/reduction of ICC is in human HSCR. Some studies of HSCR tissues have reported a reduction in the cellular density of ICC or "disrupted" ICC networks within the aganglionic region [126, 127], whereas others have observed normal ICC networks in aganglionic gut [128, 129]. These latter findings, together with the data outlined above from chick and mouse gut showing the ICC develop in gut deprived of neural crest-derived ENS precursors [22, 113, 130], suggest that ICC can develop in the absence of enteric neurons.

ENS/Smooth Muscle/ICC Developmental Interactions

Here we have outlined some key developmental aspects of gastrointestinal smooth muscle, the enteric nervous system, and ICC that together comprise the gut neuromusculature. The neurons and glia of the ENS are derived from the neural crest, whereas the smooth muscle and ICC originate from mesoderm-derived mesenchyme. In order to colonise the entire length of the gut, and become orientated into myenteric and submucosal ganglia, NCC receive essential signalling cues expressed by the developing smooth muscle. ICC, which are closely related to smooth muscle cells but critically differ in their requirement for Kit signalling, appear to be able to develop in the absence of enteric neurons, but whether they form normal, functional networks in these circumstances are still open to debate. Smooth muscle also develops in the absence of ENS cells but, in some mouse models of aganglionosis, gut muscle appears to be abnormal. Thus developmental interrelationships between these three cell types are crucial for formation of a functioning gastrointestinal tract, and a better understanding of how ENS cells, smooth muscle and ICC develop and interact will help shed light on the pathophysiology of gut neuromuscular diseases.

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Development of Gut Motility

3

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Coordinated movements of the gastrointestinal tract are crucial for the primary functions of this organ: digestion of food, absorption of nutrients, and removal of waste products. Several complex motor patterns involving coordinated contractions and relaxations of the external muscle layers of the gut have distinct roles in gut motility (see below). These motility patterns have been intensively studied and characterized in adults, but there is far less known about gut motility during development. Here we review the types of motor patterns that are present in the gut of developing laboratory animals and humans. We also discuss the mechanisms that regulate intestinal movements during development.

Motility Patterns and Their Control Mechanisms in the Mature Gut

Coordinated movements of the gastrointestinal tract include mixing, propagating motor activities, and receptive relaxation. These movements are regulated by multiple control systems including extrinsic neurons, intrinsic neurons (the enteric nervous system, ENS), interstitial cells of Cajal (ICC), PDGFRα-expressing cells, and myogenic mechanisms, which can all operate simultaneously [1–3]. The relative contribution of each control system to a particular activity varies between different regions of the gastrointestinal tract [4]. Furthermore, as discussed later in this article, recent studies in animal models also show that the relative contribution of different control systems to contractile activity in the intestine also varies with developmental age [5]. Thus, the control of gut motility is very complex [2, 6].

The primary function of the esophagus is to act as a conduit between the pharynx and the stomach, and the only motor pattern is peristalsis. During the pharyngeal phase of swallowing, the upper esophageal sphincter (UES) relaxes, and there is then a sequential contraction of esophageal muscle from the proximal to the distal end, followed by lower esophageal sphincter (LES) relaxation, so as to allow the bolus to enter the stomach. This integrated sequence of reflexes induced by swallowing constitutes *primary peristalsis* (Fig. 3.1). Peristalsis is also induced by esophageal distension, which is termed *secondary peristalsis*. In humans, the upper third of the esophagus, which is striated muscle, is controlled entirely by neurons in the brainstem via the vagus nerves. The lower, smooth muscle regions of the esophagus are controlled by the vagus nerve, intrinsic neurons, and myogenic mechanisms [4].

Different motor patterns occur in the proximal and distal stomach [4]. In the proximal stomach, receptive relaxation and accommodation occur, which are both mediated by neurons in the brainstem via vago-vagal reflexes. The distal stomach exhibits different motor patterns in the fed and fasted states. In the fed state, the distal stomach grinds and mixes. Extrinsic neurons are not essential for this contractile activity, but it can be modulated by vagal pathways.

Multiple motor patterns occur in the small and large intestines. Migrating motor complexes (MMCs) are waves of strong contractions that sweep slowly along the gastrointestinal tract and clear indigestible food, mucous, and epithelial debris in the fasted state. In humans, MMCs occur around once every 2–4 h; most originate in the distal stomach (some start in the proximal duodenum) and propagate along significant lengths of the small intestine [4]. The initiation of MMCs is modulated by vagal input and motilin released from the duodenum, while the propagation of MMCs is

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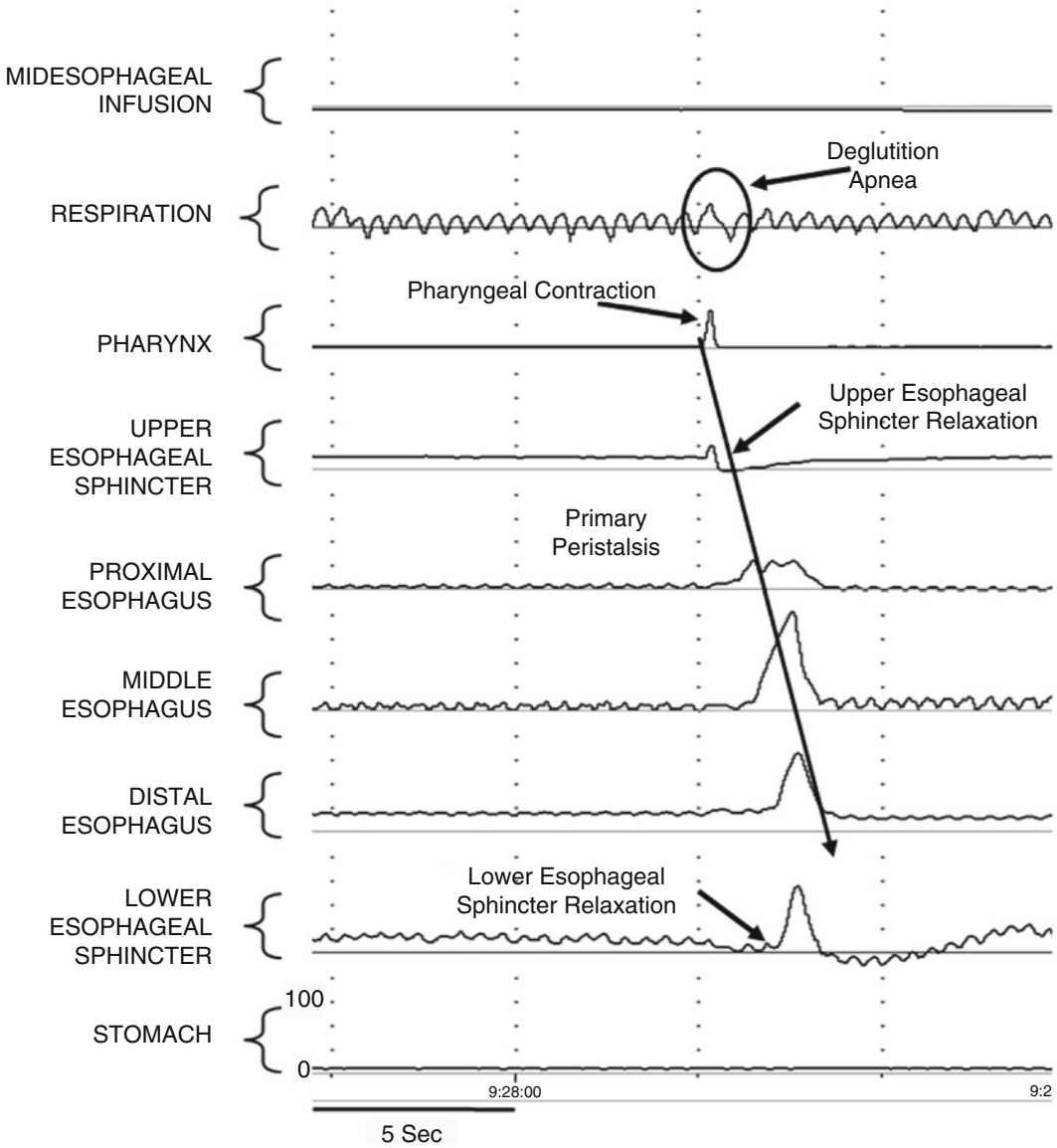

Fig. 3.1 An example of spontaneous primary esophageal peristalsis in a premature infant evoked upon pharyngeal contraction. Such sequences facilitate swallowing and esophageal clearance. Note the brief respiratory modification and deglutition apnea during pharyngeal waveform suggesting cross-communications between the pharynx and airway

coordinated by enteric neurons. In humans, MMCs occur only in the fasted state and only in the small intestine [4]. In other species, however, MMCs can occur in both the fed and fasted states and also occur in the colon.

Segmentation, alternating stationary waves of contraction and relaxation, mixes intestinal contents with digestive enzymes and exposes nutrients to the absorptive epithelium (small intestine) or facilitates water extraction (colon). Peristalsis, contraction waves that migrate in an anal direction, moves intestinal contents to new gut regions and is essential for elimination of undigested material. MMCs, which are initiated in the stomach or proximal duodenum, propagate along significant lengths of the intestine. Haustration, the mixing of feces to absorb water, occurs in saclike structures called haustrations of the large intestine of some species including humans.

Studies in animal models have shown that the ENS is essential for segmentation in the small intestine [7], although it is clear that ICC also have a major role [8]. Peristalsis in the small and large intestines is controlled by an interplay between the ENS, ICC, and myogenic mechanisms [2]. However, the ENS is essential for intestinal peristalsis as revealed by the bowel obstruction caused by the aganglionic region of infants with Hirschsprung disease [9]. The ENS is also essential for the initiation and propagation of MMCs in the small

intestine, although the CNS and hormones can modulate MMCs [4]. Studies in the rabbit colon have shown that haustral formation and propagation is neurally mediated [10]. Furthermore, water and electrolyte secretion is regulated by the ENS, as is the integration between motility and secretion [11, 12].

Development of Motility Patterns and Their Control Mechanisms: Studies of Laboratory Animals

Unlike humans, the mechanisms controlling motility patterns during development can be examined in intact segments of the gut of laboratory animals in vitro or in vivo. Most studies of mammals have been performed using segments of fetal or postnatal mouse intestine in vitro. However, because larval zebrafish are transparent, propagating contractile activity and transit studies using fluorescent food or beads have been performed in zebrafish in vivo [13–18], including studies to model and understand the pathogenesis of an inherited form of chronic intestinal pseudo-obstruction [19]. In this section we focus by necessity on the small and large intestines as there are relatively few studies on the development of motility patterns and their control mechanisms in the esophagus and stomach of laboratory animals.

Motility Patterns Present in the Developing Gut

Although fetal mammals receive nutrition solely via the placenta, contractile activity in the gut commences well before birth. The esophagus of preterm piglets (delivered by caesarean section at 91 % of full gestation) exhibits esophageal contractions in response to oral feeding, but compared to term piglets, the frequency of contractions is lower and the contractions propagate at a lower velocity [20]. In fetal mice, shallow contractions that propagate both orally and anally are first observed in preparations of small intestine in vitro at embryonic day (E) 13.5 (the gestation period for a mouse is around 19 days) [5]. Moreover, propagating contractions are observed in zebrafish larvae before the yolk sac is fully absorbed [13–16]. The physiological role of prenatal (or pre-yolk sac absorption) gastrointestinal contractile activity is unclear. Fetal mammals swallow amniotic fluid, which advances along the gut [21–23], and this meconium progresses toward the distal regions of bowel during late fetal stages [24]. Although it is highly likely that the propagating contractile activity that occurs prior to birth contributes to the propulsion of meconium anally prior to birth, this has yet to be conclusively demonstrated.

Development of Enteric Neurons and Their Role in Motility During Development

The ENS arises from neural crest-derived cells that emigrate primarily from the caudal hindbrain [25, 26], although sacral level neural crest cells also give rise to some enteric neurons, mainly in the colon and rectum [27–29]. Vagal neural crest-derived cells that colonize the colon migrate significant distances as the gut is growing as they migrate [30–32]. Neuronal differentiation commences early as pan-neuronal markers are expressed by a subpopulation of neural crest-derived cells as they are migrating along the gut in fetal mice and rats [33, 34].

In the mature ENS, there are many different subtypes of enteric neurons [35]. Prior to neuronal differentiation, precursors exit the cell cycle. Studies in mice have shown that different neuron subtypes exit the cell cycle at different developmental ages; serotonin interneurons exit the cell cycle first, at mid-embryonic ages, while some excitatory motor neurons appear to be the last neuron subtype to exit the cell cycle, around birth [36–38]. Cells expressing markers for some enteric neuron subtypes are present shortly after the first expression of pan-neuronal proteins [39], but different enteric neuron subtypes first appear at different ages [40]. The interval between cell cycle exit and the first detectable expression of enteric neuron subtype markers varies from under 2 days to around 1 week [38]. There is evidence that some enteric neurons change their phenotype during pre- and/or postnatal development [38, 41, 42].

Expression of neuronal nitric oxide synthase (nNOS—the synthetic enzyme for nitric oxide) and choline acetyltransferase (ChAT, the synthetic enzyme for acetylcholine) by developing enteric neurons has been the most extensively studied. nNOS neurons in the mature ENS include interneurons and inhibitory motor neurons to the external muscle layers [43]. ChAT neurons include excitatory interneurons and excitatory motor neurons to the external muscle layers [44]. In both zebrafish and mice, nNOS neurons are one of the first enteric neuron subtypes to appear during development [15, 39, 45, 46]. In guinea pigs, although the total number of myenteric neurons in the small intestine increases between neonatal and adult stages, the total number of nNOS neurons in the neonatal guinea pig is the same as in adults, and so the percentage of myenteric neurons expressing nNOS declines during postnatal development [47]. In zebrafish, the proportion of enteric neurons expressing nNOS does not change between 72 and 120 hpf (hours postfertilization) [46]. In the rat, however, the proportion of myenteric neurons expressing NOS increases postnatally [48]. Uptake of ^{3}[H]-choline [49] and neurons expressing ChAT [50, 51] are also present in the gut during early ENS development in the mouse. Moreover, functional nicotinic acetylcholine receptors are expressed in the mouse gut shortly after ChAT neurons develop, but the

contribution of different nicotinic acetylcholine receptor subunits to synaptic transmission changes during pre- and postnatal development [52]. In rats, the percentage of ChAT-immunoreactive myenteric neurons increases during postnatal development [48]. Changes in the proportions of some subtypes of enteric neurons have also been reported between weaning and adulthood in rats and guinea pig, suggesting that the ENS is not fully mature at weaning [53–55].

The development of the innervation of the muscle layers has been examined in a number of species. In the dog, the plexuses of nerve fibers in the small intestine and colon are immature at birth [56]. In the guinea pig ileum, the density of cholinergic nerve fibers in myenteric ganglia and in the tertiary plexus is higher at neonatal stages than in adults [47], whereas in the mouse colon the density of cholinergic nerve fibers in the circular muscle layer increases during early postnatal stages [57]. These differences might reflect the fact that mice are born at a developmentally earlier age than guinea pigs.

Many ion channels are expressed during early ENS development [58], and electrophysiological and calcium imaging studies have shown that the ENS is one of the first parts of the nervous system to show mature forms of electrical activity [59, 60]. However, studies in mice and zebrafish using pharmacological inhibitors of neural activity or mutants lacking enteric neurons have shown that the first motility patterns are not neurally mediated [5, 16]. There is therefore a significant delay between when enteric neurons first develop and when neurally mediated motility patterns are observed. This very likely reflects the fact that the neural circuitry mediating motility patterns involves at least three different types of neurons [61], which must develop and then form the appropriate synaptic connections with each other and with target cells. An ultrastructural study reported synapse-like structures in the stomach of E12.5 mice, and mature-looking synapses were present along the entire gut by E16.5 [62]. Intracellular electrophysiological recording revealed synaptic activity in many enteric neurons in newborn mice, but also showed that maturation of enteric neural properties continues for some time after birth [63]. Little is known about the molecular mechanisms regulating the formation of synapses and connectivity in the developing ENS. However, mice lacking components of the planar cell polarity (PCP) signaling pathway have defects in the axonal projections of some neurons and hence connectivity defects [64]. The PCP mutant mice are particularly interesting as they have severe motility defects including distension of the small intestine and colon, defects in the frequency of colonic migrating motor complexes (CMMCs), and defects in pellet production, but there are no changes in the density of myenteric neurons or in the density of the major neuronal subtypes [64]. It is possible that some cases of intestinal pseudo-obstruction or functional bowel disorders in infants and children are due to defects in the development of ENS circuitry, and such defects cannot be detected by standard pathological testing.

In mice, neurally mediated motility patterns are not observed until shortly before birth in the duodenum [5] and a week after birth in the colon [57]. In longitudinal colonic muscle strips from postnatal rats, electrical field stimulation-induced contractions are reduced by a muscarinic acetylcholine receptor antagonist starting at postnatal day (P) 14, whereas inhibition of nNOS caused a significant increase in the contractile response only from P36 [48]. Thus, cholinergic neuromuscular transmission to the longitudinal muscle in the rat colon does not develop until postnatal stages and precedes the development of nitric oxide-mediated transmission. In the mouse small intestine, cholinergic neuromuscular transmission commences at late fetal stages [65]. In contrast, cholinergic neuromuscular transmission in the guinea pig taenia and in the frog gut commences after inhibitory or nitric oxide-mediated transmission [66, 67]. In the longitudinal muscle of human and guinea pig intestine, nitric oxide-mediated transmission is relatively more prominent at postnatal stages than in adults [47, 68].

Neurotransmitters and neurotransmitter-related substances released or expressed by enteric neurons that differentiate early appear to influence the later development of the ENS [31, 69, 70]. For example, mice lacking tryptophan hydroxylase 2 (TPH2), the enzyme required for the synthesis of serotonin by neurons, have decreased myenteric neuron density; as serotonin neurons are generated early during ENS development (see above), it appears that release of serotonin by some of the first neurons to differentiate promotes the differentiation of ENS precursors [69].

In summary, although enteric neurons develop early, the first gastrointestinal motility patterns are not neurally mediated. However, neurally mediated contractile activity is prominent in the upper small intestine of the mouse by birth and is essential for propulsive activity in the colon of newborn humans as shown by the bowel obstruction that occurs proximal to the aganglionic region in infants with Hirschsprung disease. One of the first subtypes of enteric neuron to develop is the nNOS neurons, and although there are some exceptions, nitric oxide-mediated transmission develops earlier and/or is more prominent during pre- and postnatal development than in adults. As the relative importance of different neurotransmitters to gastrointestinal contractile activity changes significantly during development, drugs that successfully treat motility disorders in adults will not necessarily have similar effects in infants and children.

Development of Fibroblast-Like Interstitial Cells (Including Kit + Interstitial Cells of Cajal (ICC) and PDGFRα + cells) and Their Role in Motility During Development

Diverse populations of fibroblast-like interstitial cells are present in the adult gut. Loss or dysfunction of these cells has been linked to a wide variety of gastrointestinal disorders including achalasia [71, 72], gastroparesis [73–76], infantile hypertrophic pyloric stenosis [77], idiopathic chronic intestinal pseudo-obstruction [78], and slow transit constipation [79, 80]. This broad group of cells comprises various subpopulations of Kit-positive interstitial cells of Cajal (ICC) and fibroblast-like cells that express platelet-derived growth factor receptor alpha (PDGFRα).

ICC located at the level of the myenteric plexus (ICC-MY) mediate slow waves, the electrical events that time the occurrence of phasic contractions [81–84], while evidence is accumulating that ICC and PDGFRα + cells located within and surrounding gastrointestinal muscle bundles serve as intermediaries in both excitatory and inhibitory neuromuscular transmission [85–87].

Unlike enteric neurons and glia, ICC do not arise from the neural crest during embryological development as ICC develop in explants of avian and mammalian embryonic gut which have been removed prior to the arrival of neural crest cells in that region [88, 89]. Furthermore, ICC are distributed normally, and slow-wave activity is generated in the bowel of mutant mice lacking enteric neurons [90, 91]. Hence, ICC development and maintenance are independent of neural crest-derived cells in mice. In an infant with intestinal aganglionosis extending into the jejunum, abundant ICC were present in the myenteric region, but degenerating ICC were observed in the circular muscle of the aganglionic region [92]. Thus, in humans, ICC also arise independently of neurons, although some subpopulations of ICC may directly or indirectly require neurons for their long-term survival.

Developmental studies in mice suggest that smooth muscle cells and ICC arise from a common mesenchymal precursor following a process of epithelial-mesenchymal transition (EMT) [93–95]. Both ICC and CD34+ fibroblast-like cells derive from the coelomic epithelium, most likely from a common progenitor expressing the chloride channel anoctamin-1 and smooth muscle actin alpha [95]. Differentiation to the ICC phenotype during embryogenesis is dependent upon cellular signaling via the tyrosine kinase receptor, Kit [65, 94, 96, 97]. The natural ligand for the Kit receptor is stem cell factor (SCF or *steel*), which is expressed in both enteric neurons and smooth muscle cells [90, 91, 98]. Mutations leading to deficiency of Kit in *W/Wv* mice or membrane-bound SCF in *Sl/Sld* mice result in disruptions of particular ICC populations and aberrant gastrointestinal motility [81–83]. Both migrating motor complexes and higher-frequency phasic contractions can be recorded from the small intestine of *W/Wv* mice, which lack intestinal ICC-MY [99], but the phasic contractions are characteristically abrupt and uncoordinated [100]. Treatment of embryonic jejunal explants with Kit-neutralizing antibodies prior to the emergence of cells with the ultrastructural characteristics of ICC prevents the development of ICC and slow-wave activity [65]. The postnatal maintenance of ICC also appears dependent upon Kit signaling as injection of Kit-neutralizing antibodies resulted in loss of ICC and lethal paralytic ileus in neonatal mice [97]. Loss of ICC due to Kit blockade is accompanied by a loss of electrical slow-wave activity in the small intestine and reduced neural responses in the small bowel and colon [101]. In the absence of Kit signaling, ICC appear to differentiate to a smooth muscle phenotype but appear to retain, at least in the short term, the ability to regenerate the ICC phenotype if Kit signaling is restored [96].

During embryogenesis there is a rostral-to-caudal development of ICC along the gastrointestinal tract. In embryonic mice, the circular muscle layer differentiates prior to the longitudinal muscle layer [94]. Nearly all of the mesenchymal cells between the serosa and the newly formed circular muscle layer, consisting of precursors of both longitudinal muscle and ICC, initially express Kit [65, 101]. As embryonic development progresses, a subpopulation of these mesenchymal precursors lose expression of Kit and differentiate into longitudinal smooth muscle [94]. The Kit-positive cells on the circular muscle side of this newly formed longitudinal muscle layer develop into the anastomosing network termed ICC-MY.

Motility patterns of the stomach during development have not been extensively researched using laboratory animals. In mouse, 2 days prior to birth, ICC-MY and slow-wave activity are present in the gastric antrum, while spindle-shaped intramuscular ICC (ICC-IM) are evident, and neurally mediated responses can be recorded from the gastric fundus [102].

Intramuscular ICC (ICC-IM) are closely associated with the varicose terminals of both excitatory and inhibitory motor nerves of the stomach, small intestine, and colon [85, 86, 103, 104], and in gastric tissues lacking ICC-IM, neural transmission from enteric motor neurons is significantly compromised [85, 86, 105]. Despite the close anatomical arrangement between nerves and ICC-IM, the outgrowth of motor nerve processes does not appear to be dependent upon the presence of ICC as the distribution of both excitatory and inhibitory nerve processes is normal in *W/Wv* fundus muscles devoid of ICC-IM [86, 105]. In contrast, the terminal processes of vagal intramuscular arrays do not ramify within the circular muscle layer of the stomach in the absence of ICC-IM [106, 107].

Electrical rhythmicity can be recorded from segments of mouse small intestine 3 days prior to birth [65, 96]. However, the first propagating contractions in mouse intestine are evident in the mid-stages of embryonic development (embryonic

day 13), prior to the emergence of a Kit-positive ICC network and slow-wave activity at embryonic day 18 [5]. The frequency of these initial contractions is similar in wild-type mice and in mutant (*W/Wv*) mice lacking ICC-MY, providing further evidence that these contractile patterns are myogenic (In the field of gastrointestinal motility, the term "myogenic" has been used to describe contractile activity generated by ICC as well as muscle cells, but here we use the term myogenic to refer to contractions specifically originating from the muscle cells themselves) rather than ICC mediated. Closer to the time of birth, after anastomosing networks of ICC-MY have been established, slow waves and phasic contractions occur at a similar frequency suggesting that myogenic contractions become entrained by ICC-MY [5]. Around 5 days after birth, a second layer of Kit-positive cells, termed ICC-DMP, is present in the region of the deep muscular plexus of the rodent small intestine [94, 102, 108–110]. ICC-DMP in the small intestine and ICC in the region of the submucosal plexus in the colon (ICC-SMP) arise from smooth muscle progenitors expressing leucine-rich repeats and immunoglobulin-like domains protein 1 (LRIG1) [111]. Loss of LRIG1 expression results in loss of ICC-DMP and ICC-SMP but preservation of ICC-MY suggesting that LRIG1 plays an essential role in the differentiation of smooth muscle progenitors to subpopulations of Kit-expressing ICC [111]. Development of neuromuscular responses to stimulation is concomitant with the development of ICC-DMP, and blockade of ICC-DMP development with Kit-neutralizing antibodies has been shown to lead to a severe attenuation of postjunctional responses to nerve stimulation [110] suggesting their role as mediators of neurotransmission in the intestine. More recently it has been suggested that Ca^{2+} signaling within ICC-DMP underlies the motor pattern of segmentation within the small intestine [8]. Interestingly, intestinal transit is delayed and the abdomen becomes distended in LRIG1-null mice lacking ICC-DMP suggesting these cells serve a functionally significant role in intestinal physiology [111].

Kit-negative fibroblast-like interstitial cells within the gastrointestinal tract have been described for many years [112–115]. However, the recent discovery that PDGFRα provides a reliable biomarker of these cells has accelerated investigations into their distribution and functional role within the GI tract [116]. PDGFRα-positive interstitial cells have been described in various regions within the rodent, primate, and human gastrointestinal tract including within the plane between the muscularis mucosae and the circular muscle layer and within circular muscle bundles—where they are located in close proximity to excitatory and inhibitory nerve terminals, Kit-positive ICC, and smooth muscle cells [87, 104, 117, 118]. It has been proposed that PDGFRα + cells mediate inhibitory inputs from purinergic nerves as, in addition to being closely apposed to motor nerve terminals, they are enriched in components required for the detection and transduction of purinergic signals [119] and exhibit calcium transients and large amplitude apamin-sensitive K+ currents in response to exogenously applied purines [87, 120]. It is possible that the CD34+ fibroblast-like population of cells that are reduced in a form of chronic intestinal pseudo-obstruction [121] are the PDGFRα cells described by others [118]. The developmental progenitors of PDGFRα + cells and the timing of their differentiation within the gastrointestinal tract remain to be determined.

Role of Myogenic Mechanisms in Intestinal Motility During Development

Studies in embryonic mice and zebrafish have shown that the first intestinal motility patterns to appear during development, spontaneous contractions that propagate anally and orally, are not mediated by neurons or ICC [5, 16]. Hence, the contractions must be myogenic, that is, generated by the smooth muscle cells themselves. Motility patterns that are not mediated by either neurons or ICC are present in the intestine of mature animals but under normal conditions are not very prominent [122, 123]. However, propagating contractions in other organs of mature animals, including the upper urinary tract, vas deferens, and uterus, are entirely myogenic in origin [124]. In the duodenum and colon of fetal mice, the myogenic contractions require the entry of extracellular calcium [5], but it is unknown how they are initiated or propagated.

Environmental Influences on Motility Patterns During Development

In the adult gut, specific nutrients can change the function and phenotype of the ENS [125]. The composition of gut contents changes dramatically immediately after birth and then at weaning, and it is likely that these changes induce changes in motility patterns. Daily butyrate enemas performed on 7-day-old rats for 10 days did not affect body weight, histological appearance of the colon, or the number of myenteric neurons/ganglion but did induce increases in the proportion of neurons expressing markers of cholinergic neurons and nitric oxide neurons and increases in distal colonic transit time [126]. There is evidence from piglets that the introduction of solid food at weaning induces changes in some of the properties of MMCs [127]. Dietary components are also known to affect motility and gene expression in the ENS of mature rats; in particular, long-term exposure to resistant starch diet enhanced colonic propulsive motility and increased the number of ChAT-immunoreactive myenteric neurons [128].

After birth, the gut is colonized by a vast number of microbes, known as the gut microbiota. Studies using animals lacking a microbiome have shown that, in addition to

aiding food processing, the microbiota influences the nervous system including the brain [129]. The microbiota also plays important roles in the development of the ENS. Mice lacking a microbiome possess less glial cells in the mucosa [130] and fewer myenteric neurons but a higher proportion of nitric oxide synthase neurons [131]. Within the colon of developing mice, it appears that LPS-mediated activation of toll-like receptors during gestational development is required to maintain normal populations of nitrergic inhibitory nerves [132]. Moreover, piglets treated with a probiotic show increases in the expression of some neurotransmitters in submucosal, but not myenteric, neurons [133].

Motility can also be altered by more general insults. For example, the transit of fluorescein-labeled luminal contents along the small intestine of fetal rabbits is decreased after a 1-h hypoxic episode [23].

Motility in Human Neonates and Children

In human infants, gastrointestinal motility is very complex and, as in laboratory animals, is almost certainly influenced by maturational changes in the CNS and ENS, gut muscle, and ICC, as well as diet and changing anatomical postures during infancy. Furthermore, in the vulnerable high-risk infant in intensive care units, hypoxia, inflammation, sepsis, and other comorbidity conditions can complicate the feeding process and gastrointestinal transit.

Immunohistochemical studies of human fetuses have shown that neurons, muscle, and ICC differentiate from proximal to distal and that the longitudinal and circular muscle layers and myenteric and submucosal plexuses have a mature appearance by week 14 [134, 135]. As in laboratory mammals, many subtypes of enteric neurons develop prior to birth [40]. Kit-expressing ICC-MY first appear around weeks 7–9 [134, 135]. In the stomach, ICC-MY, ICC-IM (intramuscular), and ICC-SEP (ICC located within connective tissue septa separating muscle bundles) are all present by the end of the fourth month of development [136].

The simple physiological functions of the neonatal foregut, midgut, and hindgut, respectively, are to facilitate (1) safe feeding by steering ingested material away from the airway, (2) gastrointestinal transit and mixing of luminal contents to permit absorption and propulsion, and (3) evacuation of excreta to modify the intestinal milieu. In this section on human neonates, we will review the developmental aspects of (1) pharyngoesophageal motility, (2) gastric motility, (3) small intestinal motility, and (4) colonic motility. In particular, we will also review recent advances and discoveries.

The concept of reciprocal interactions between aerodigestive systems, enteric nervous system, and central nervous system is increasingly gaining importance across the age spectrum, and the developmental and maturational aspects of these entities are highlighted. Specifically, recent advances in the field of developmental aerodigestive reflexes and gastrointestinal motility are briefly discussed in the following sections and fully referenced.

Developmental Pharyngoesophageal Motility in Human Neonates

Swallowing Prior to Birth

Numerous studies have shown that the human fetus swallows amniotic fluid [21, 137]. By 11 weeks of gestation, the ability to swallow has developed and by 18–20 weeks sucking movements appear. There is an increase in the volume swallowed with gestational age, and by near term, the human fetus swallows around 500 mL of amniotic fluid per day [137]. Studies using a sheep model have shown that, as in adults, swallowing in near-term fetuses involves central cholinergic mechanisms [138].

Upper and Lower Esophageal Sphincter Functions and Esophageal Peristalsis in Human Neonates

Using micromanometry methods, the upper esophageal sphincter (UES), esophageal body, and lower esophageal sphincter (LES) functions have been characterized in neonates [139–141]. The resting UES tone increases with maturation from around 18 mmHg in 33-week preterm infants to 26 mmHg in full-term born neonates compared to 53 mmHg in adults. In contrast, the motor events associated with LES relaxation in healthy preterm infants 33 weeks and older have similar characteristics to adults [142].

In 33-week preterm infants, primary esophageal peristalsis occurs, but considerable maturation occurs pre- and postnatally [139, 141]. For example, evaluation of consecutive spontaneous solitary swallows in preterm infants at 33 weeks, preterm infants at 36 weeks, full-term infants, and adults showed significant age-dependent changes in the amplitude and velocity of the peristaltic contractions [140].

During anterograde movement of a bolus following swallowing or during retrograde movement of a bolus during gastroesophageal reflux events, the bolus comes in close proximity to the airway. Peristalsis is the single most important function that ensures clearance of luminal contents away from the airway. During primary esophageal peristalsis, there is a respiratory pause called deglutition apnea that occurs during the pharyngeal phase of swallow (Fig. 3.1). This brief inhibition in respiration is due to a break in respiratory cycle (inspiratory or expiratory) and is a normal reflex. On the other hand, during esophageal provocation events (e.g., infusion via a manometry catheter or gastroesophageal reflux), proximal esophageal contraction and distal esophageal relaxation result in secondary peristalsis, which occurs

independent of central swallowing mechanisms (Fig. 3.2) [143–145]. These reflexes prevent the ascending spread of the bolus and promote descending propulsion to ensure esophageal clearance.

Secondary esophageal and UES contractile reflexes have been compared in 33-week and 36-week mean postmenstrual-age premature infants [146]. The occurrence of secondary peristalsis was volume dependent, and the characteristics matured with age. Furthermore, as the premature infant grew older, the occurrence of secondary peristalsis increased significantly with increment in dose volumes of air or liquids. Thus, it appears that vago-vagal protective reflex mechanisms that facilitate esophageal clearance are present in healthy premature neonates, but these mechanisms mature with age.

Esophageal provocation can also result in an increase in UES pressure [143, 144]. This reflex is the *esophago-UES-contractile reflex* and is mediated by the vagus. The UES contractile reflex has been studied in premature infants, and like secondary peristalsis, the occurrence of UES contractile reflex is volume dependent, and the reflex matures during

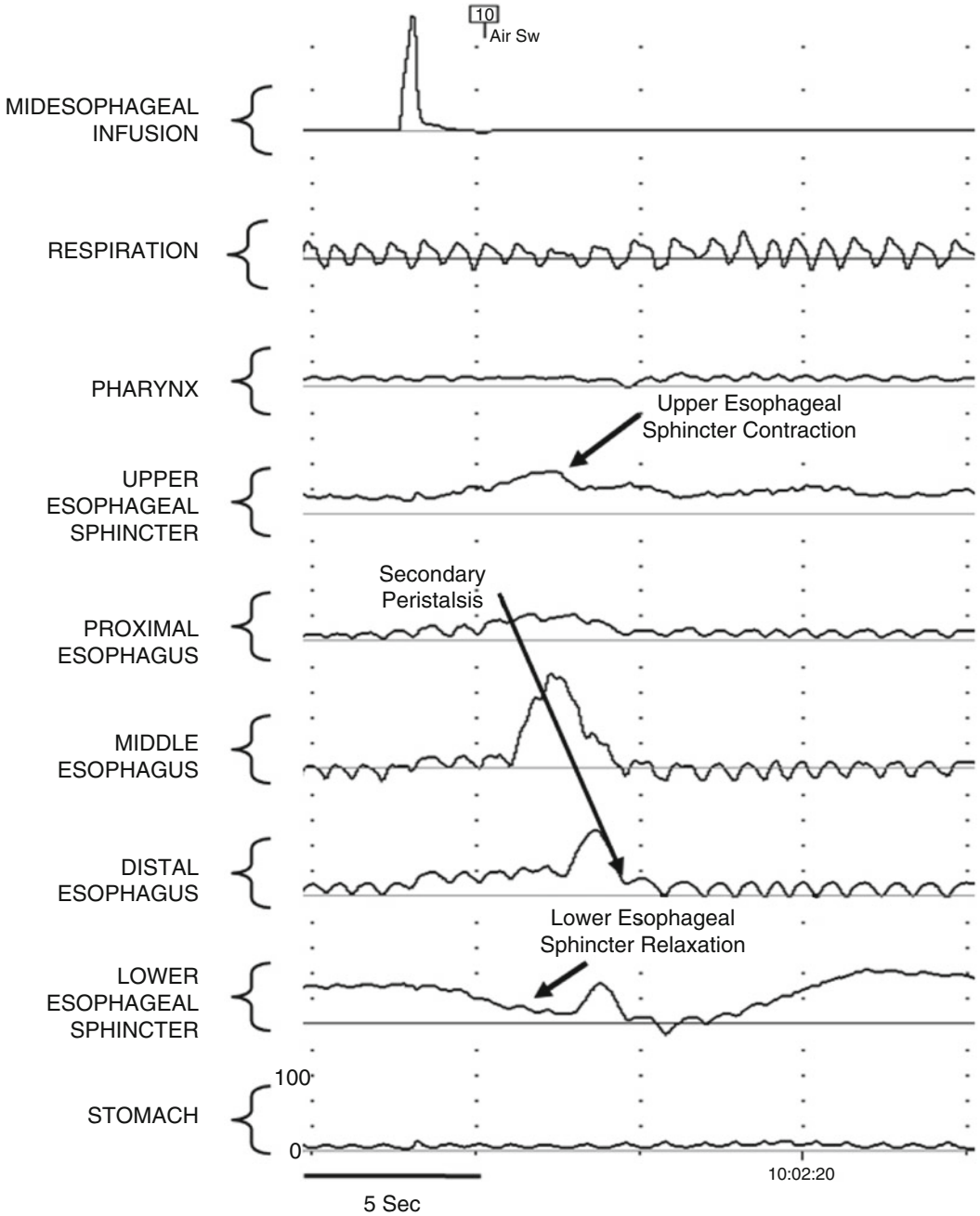

Fig. 3.2 Swallow independent secondary esophageal peristalsis in a premature infant in response to a mid-esophageal infusion. Such sequences are evoked during esophageal provocations and contribute to esophageal and airway protection by facilitating clearance

Table 3.1 Infant esophageal motility characteristics in health and disease

Organs	Controls	Preterm	Neurological disorders	HIE in full term
Upper esophageal sphincter	• Intact airway protective contractile and relaxation	• Intact contractile and relaxation kinetics	• Increased UES resting pressure	• Increased magnitude of UES contraction
	• Contraction, most common response to esophageal stimulation		• Increased maximum contractile pressure	
	• Relaxation, most common response to pharyngeal stimulation		• Increased contraction magnitude	
			• Most rapid response sensitivity resulting in contractile reflex	
Peristaltic reflexes	• Recruited upon stimulation of the mid-esophagus	• Primary peristalsis is recruited more frequently with esophageal bolus	• Prolonged reflex response latency to liquids	• Secondary peristalsis is the primary clearance mechanism upon esophageal stimulation
	• Secondary peristalsis is primary mechanism	• Secondary peristalsis increases with maturation	• Secondary peristalsis is the primary clearance mechanism upon esophageal stimulation	
	• Pharyngeal reflexive swallowing during pharyngeal stimulation			
Esophageal body	• Exhibit anterograde muscle contractile activity in response to a bolus	• Decreased peristaltic velocity	• Increased amplitude and prolonged duration of esophageal contraction	• Prolonged peristaltic duration
		• Amplitude and esophageal contraction duration are similar with controls		• Increased polymorphic waveforms
Lower esophageal sphincter	• Relaxes during either basal or adaptive swallowing	• Relaxation reflexes intact	• *Decreased* duration of LES relaxation	• Lower (−) nadir pressure and prolonged duration of relaxation
	• As infant matures, relaxation magnitude increases and duration decreases		• *Increased* nadir duration	

postnatal age. This reflex may provide protection to the airways by limiting the proximal extent of the refluxate during spontaneous gastroesophageal reflux events. The summary of aerodigestive reflex characteristics in health and disease are shown in Table 3.1.

Aerodigestive Motility Reflexes, Threatening Events, and Sleep States

Neonates and infants sleep for more time than they are awake, and this ratio decreases in favor of more wakeful periods during maturation. Sleep is a physiological state wherein there is excessive inhibition or suppression of the effects of somatic and visceral stimuli from reaching central neural pathways, regulated by the reticular activating system and may be related to elevated sensory thresholds. However, the organism is vulnerable to internal and external threats and must respond to maintain homeostasis. Aerodigestive provocation and risk for aspiration are of frequent threats in infants; such risks are more so in the situations of immaturity, neuropathology, chronic lung disease, gastroesophageal reflux disease, and/or during sleep. Aerodigestive provocation is essential and critical during swallowing or during gastroesophageal reflux events. Newborn infants may sleep up to 80 % of the time, and arousals from sleep have been considered important central awareness and protective responses in infants [147]. Premature infants can perceive visceral sensitivity during anterograde esophageal transit as in swallowing, associated with activation of cortical and subcortical arousal mechanisms [148]. Perceived threat is more with gastroesophageal reflux events extending proximally and retrograde transit resulting in heightened excitation and prolonged activation of cortical pathways [148].

However, lack of arousals does not mean inadequate aerodigestive protection. Other aspects of regional and local reflexes are contributory to thwart the stimulus away from the introitus and prevent its ascending spread while maintaining sleep. Sensory effects of esophageal mechanosensitivity, osmosensitivity, and chemosensitivity are progressively

advanced in sleep during maturation as evidenced by increased frequency recruitment of motor responses [149]. With growth and development, premature infants are better able to handle provoking stimuli and avoid sleep disturbances as they age, which may also be attributed to somatic changes in esophageal length preventing proximal migration of the stimulus. Sleep modulates the frequency recruitment and type of aerodigestive reflexes [149].

The incidence of apparent life-threatening events varies from 0.5 to 6 % and accounts for about 1 % of emergency visits [143, 150, 151]. In such infants, prolonged spontaneous respiratory disturbing events as evident by apneic events >2 s or at least two missed breaths or changes in cardiac and respiratory rhythms have been associated with ineffective esophageal motility, which are suggestive of dysfunctional regulation of swallow-respiratory junction interactions, activation of exaggerated pharyngo-glottal closure reflexes, or esophagoglottal closure reflexes. Thus, inciting and stimulus-provoking responses underlie in the proximal aerodigestive tract [150].

In summary, the frequency of gastroesophageal reflux events as well as physical and sensory symptoms is lower during sleep [152]. Sleep is associated with inhibition of the reticular activating system, resulting in elevated sensory threshold. The frequency of physical and sensory symptoms is less during sleep. Cardiorespiratory symptoms during sleep are not likely to be related to gastroesophageal reflux disease (GERD) causes. Mechanism of symptom generation and adaptation are different during sleep and wake states, underscoring the differential ability of infants to perceive esophageal sensitivity during sleep [152].

Mid-esophageal stimuli provoke arousals more than 50 % of the time, which are associated with altered esophageal responses, increased respiratory arousals, and frequent sleep state changes [148]. However, the latency response durations of peristaltic reflexes and UES contractile reflexes are prolonged and more frequently associated with cortical hypervigilance [148]. With maturation, an ability to handle provoking stimuli and avoid sleep disturbances occurs and may be attributed to brainstem maturation or increase in esophageal length that prevents more proximal migration of provocative stimuli [149]. Although the sensitivity to stimuli is well developed in premature infants, the frequency of defense mechanisms is better with maturation [149].

Effects of Maturation on Foregut-Airway Interactions

Pharyngeal stimulation occurs primarily during oral bolus propulsion or during proximal ascent of the gastroesophageal refluxate, and pharyngoesophageal reflexes are activated. Pharyngeal reflexive swallow is the most frequent response, which is often associated with the pharyngo-lower esophageal sphincter-relaxation reflex. The sensory-motor properties of pharyngeal reflexive swallowing are similar during longitudinal maturation; however, LES relaxation properties accelerate and become robust with age implying the maturation of inhibitory pathways at LES [153]. Furthermore, the infant esophagus has the discriminatory ability to distinguish gas vs. liquid stimuli, in that the liquids result in an increase in recruitment and magnitude of LES relaxation, as well as its decreased duration [153]. Thus, with age, liquids are cleared more efficiently, and peristaltic reflexes are more robust in function and may be related to better coordination of excitatory and inhibitory pathway functions.

Comparing the development and maturation of the upper esophageal sphincter and esophageal body across the age spectrum, we found that preterm infants at a young age had a decreased frequency of solitary propagated swallows/min compared to full-term infants [154]. In addition, when compared with adults, all groups of infants showed decreased resting UES tone, decreased magnitude of UES relaxation, increased duration of UES relaxation, increased UES relaxation nadir, and increased UES residual nadir pressure [140]. Infants also generally had decreased esophageal contractile amplitudes compared with adults, but these amplitudes were similar among the infant groups. Peristaltic velocity from proximal to distal esophagus was slower for preterm infants across longitudinal maturation and remained slower when compared at later age with full-term born infants [140]. Thus, all these neuromotor activities suggest that sensory-motor neuromotor and muscular functions continue to develop and adaptational responses mature through infancy and childhood.

When preterm-born infants were studied at term equivalent postmenstrual age for esophageal stimulation-induced reflexes, it was found that former very-preterm infants have characteristics approaching those of infants born closer to term with regard to UES contractile reflex latency and duration. Response latency to UES contractile reflex decreases with increasing birth gestation; thus, with increased prematurity comes an increased risk of aspiration [154]. Active LES relaxation reflex duration was prolonged, i.e., increased duration to achieve full LES relaxation, with liquid stimuli (vs. air) in former very-preterm infants but not so for later-born preterm infants. With increasing birth gestation, in response to liquid stimuli, comes decreasing LES relaxation response latency and prolonged duration of active LES relaxation. Collectively, these new discoveries reveal that the potential modulators to the underlying mechanisms may include myelination or consequences and comorbidities of prolonged NICU stress [154].

Effects of Perinatal Asphyxia on Foregut Motility Mechanisms

Perinatal asphyxia has effects on the central and enteric nervous systems, as well as on regulation of aerodigestive biorhythms. Infants with birth asphyxia are at increased risk for oromotor dysphagia, pharyngoesophageal dysmotility, and gastrointestinal dysmotility. Surviving infants are at increased risk for gastroesophageal reflux and emesis, as well as for anterograde or retrograde aspiration. Such infants need chronic tube feeding strategies owing to inadequate peristaltic coordination of oromotor, pharyngoesophageal, and gastrointestinal motility. The mechanisms for such maladaptation are now increasingly clear. For example, infants with perinatal asphyxia differ from healthy controls in demonstrating increased resting UES tone, decreased LES nadir pressure, increased LES nadir duration, increased peristaltic duration, more frequent polymorphic waveforms, more frequent occurrence of secondary peristalsis, and increased magnitude of the UES contractile reflex [155]. Potential mechanisms of dysfunction include ischemia-reperfusion injury to brain stem-mediated adaptational responses or inappropriate alteration of neurotransmitter release and or activity.

Effects of Perinatal Asphyxia on Adaptive Swallowing Reflexes

Infants with perinatal asphyxia have dysphagia and frequent aerodigestive problems, but the mechanisms of such symptoms remain difficult to clarify. Therefore, the available diagnostic work-up or modifications in therapies are questionable. To understand the mechanisms of feeding dysfunction, we studied infants with perinatal asphyxia [156]. Notably, infants with HIE compared with healthy controls had increased UES resting tone and increased occurrence of the pharyngo-UES contractile reflex in lieu of pharyngeal reflexive swallow, which is the most frequent reflex in health [156]. In addition, these infants displayed increased recruitment of pharyngeal peaks per stimulus, increased duration to restore aerodigestive quiescence, increased presence and duration of polymorphic waveform activity, decreased proximal esophageal contractile amplitude and increased contractile duration, increased mid-esophageal contractile duration, decreased LES resting tone, decreased frequency of pharyngo-LES relaxation reflex, and increased LES nadir duration [156]. Potential mechanisms include summation of contractions in a phenomenon similar to tetanic contraction or hypoxic exposure blocking the release of acetylcholine at the neuromuscular junction [156].

Gastric Motility in Human Neonates

Scant information is available about receptive relaxation in the fundus in human neonates. Ultrasound studies of the fetal stomach detected gastric emptying as early as 13 weeks of gestation [157], and the length of gastric emptying cycles in fetuses increases just prior to birth [158]. The rate of gastric emptying is not influenced by non-nutritive sucking, but is influenced by calorific value and stress: Calorically denser formula accelerates gastric emptying and extreme stress, such as the presence of systemic illness, and delays gastric emptying [159].

Evaluation of Gastroesophageal Reflux

Gastroesophageal reflux is the physiological passage of gastric contents into the esophagus affecting 10.3 % of infants in freestanding children's hospitals in the USA [160]. Under- or overdiagnosis of gastroesophageal reflux has been noted to be associated with an increased length of stay and hospital costs [160]. To aid the evaluation of troublesome symptoms consistent with GERD, esophageal pH-impedance studies along with symptom correlation are the current gold standard. Esophageal manometry studies may aid in the characterization of potential mechanisms that may lead to symptom occurrence. Utilizing a pH-impedance probe that is passed transnasally through the esophagus provides the ability to identify detailed physicochemical and spatiotemporal characteristics of refluxate. Each ascending refluxate that is observed during the 24 h pH-impedance tracings is distinct. The content can be acidic (pH<4) or weakly acidic (pH>4). It could also be liquid reflux, a gaseous reflux, or a combination of liquid and gaseous reflux. The proximal extent and the duration of refluxate are yet another varying parameter and may be related to esophageal peristaltic motility reflexes, bolus clearance mechanisms, and acid-neutralization mechanisms.

When the relationship between height and duration of specifically acid reflux was studied, it was found that acid reflux was predominantly reaching the distal esophagus more frequently than ascending proximally [161]. However, the occurrence and frequency of symptoms and the height and clearance time of the acid are directly related [161]. Similarly, it has been shown that symptoms in GERD are not only dependent on the proximal extent and duration of dwell of refluxate but also the physical and chemical composition of reflux events [162]. Additionally, feeding plays a crucial role in the occurrence and frequency of gastroesophageal reflux [163]. Prolonged feeding durations and slower flow rates are shown to be associated with a decreased frequency of gastroesophageal reflux. While observing feeding methods, orally fed infants had more gastroesophageal reflux than gavage-fed infants [163].

Although the relationship between symptom and reflux is still unclear in preterm neonates, many attempts have been made to better the diagnostic techniques for the proper diagnoses of gastroesophageal reflux—hoping to ease the burden of troublesome symptoms.

Small Intestinal Motility in Human Neonates

In 28–37-week gestation preterm infants, the majority of the contractile activity in the small intestine consists of clusters of low-amplitude contractions that propagate for a short distance or not at all [164]. Propagating, cyclical MMCs with clearly defined phases develop between 37 weeks and term [165].

In adults, motilin, which is released from mucosal cells in the duodenum, is an important regulator of MMCs, and initiation of phase III of the MMC (intense rhythmic contractions) in the antrum is correlated with an increase in plasma concentrations of motilin [4]. In human neonates, the fasting plasma concentrations of motilin are similar to those in adults, but there are no detectable increases in motilin levels coincident with the initiation of MMCs [166]. The antibiotic, erythromycin, is also a motilin receptor agonist and accelerates gastric emptying in adults [167]. Erythromycin triggers initiation of the MMC in preterm infants whose gestational ages exceed 32 weeks [168]. Administration of erythromycin fails to trigger MMCs in infants younger than 32 weeks, suggesting immaturity of the neuronal circuitry mediating MMCs or that the motilin receptor cannot be activated by erythromycin at these ages.

Gastroduodenal Motility

Migrating motor complexes (MMC) during fasting assist in luminal content propagation throughout the gastroduodenal tract and are induced by both motilin receptor and non-motilin receptors and are likely hormonal or neutrally regulated [168–171]. MMCs consist of three phases including (a) phase I characterized by motor quiescence, (b) phase II characterized by irregular bursts, and (c) phase III characterized by intense contractile bursts with distal propagation [168]. In infants, during phase III, motilin receptor-mediated MMCs occur by 32-week gestation, while non-motilin-mediated responses are not observed until term [168]. In infants with immature foregut motility, these MMCs are often rare and/or non-propagating, but improve with maturation [164–166, 172, 173]. Erythromycin has been shown to increase MMC frequency and amplitude of the burst and thus accelerate gastric emptying [167, 174, 175]. Although erythromycin has been proven to improve gastroduodenal motility in healthy preterm infants [168, 176, 177], it does not improve gastrointestinal function in feeding intolerant preterm infants [178].

Developmental Colonic Motility in Human Neonates

There is a marked lack of data on colonic motility in neonatal humans owing to technical limitations and ethical concerns.

Mechanisms Controlling Motility in Human Infants and Children

As in laboratory animals, enteric neurons and ICC appear to be essential for normal motility in human infants and children. An essential role for enteric neurons in gut motility after birth is best demonstrated by Hirschsprung disease, where the segment lacking enteric neurons is unable to propel gut contents. Genetic alterations of Kit, and reduced ICC density, have recently been directly linked to a severe case of idiopathic constipation and megacolon in a 14-year-old child [179], demonstrating the critical relationship between Kit function, ICC development, and functional gastrointestinal motility patterns in the human intestine. Other studies have reported alterations in ICC networks in Hirschsprung's disease, chronic idiopathic intestinal pseudo-obstruction, and pediatric constipation [180–186], but these defects may be an indirect consequence, rather than the cause, of the gut dysfunction. However, it is important to remember that motility disorders in children are not necessarily due to defects in neurons or ICC. For example, X-linked intestinal pseudo-obstruction has been shown to be a myopathy and is caused by mutations in *FLNA*, which encodes filamin-A [187]. Studies in mice have also shown that defects in the gut muscle can also result in motility defects [188].

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Visceral Sensitivity

4

Christophe Faure and Franziska Righini Grunder

The central nervous system (CNS) continuously receives information from the gastrointestinal (GI) tract related to the state of the organs and to the content of the gut. CNS must integrate this information with input from other organs or from the environment in order to initiate suitable responses. The amount of information is so high that normally most of this information originating from the GI tract do not reach the level of conscious perception and is processed in the brainstem, below cortical level. Sensations such as hunger, fullness, satiety, bloating, focal gut distension, and need to defecate (as well as their physiological correlates, i.e., gastric and rectal distension) that implicate an adapted behavior do reach the cortex.

Gastrointestinal pain is reported as dull, vague, and diffusely localized. Stimuli for visceral pain include distension or traction on the mesentery as well as ischemia and inflammation that stimulate afferent nerve terminals. Cutting and crushing (e.g., mucosal biopsy sampling) of the GI tract are not perceived when applied to conscious subjects.

Abnormal heightened visceral sensitivity may lead to abdominal pain and functional GI disorders (FGID). Visceral hypersensitivity is considered as a central pathophysiological mechanism of FGID [1]. This chapter covers the physiology of the visceral sensitivity and reviews the pathophysiology and mechanisms of visceral hypersensitivity.

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Neuroanatomy and Processing of Gastrointestinal Tract Sensitivity

Visceral Innervation

Similar to somatic sensitivity, gut afferent signals reach conscious perception through a three-neuron chain (Fig. 4.1). Extrinsic innervation of the GI tract is composed of vagal afferents, spinal visceral afferents, and sacral afferents [2]. These nerves contain efferent fibers that transmit information from the CNS to the gut and afferent (or sensory) fibers that transmit information from the viscera to the CNS. Visceral afferent fibers are composed of sensory neurons that, arising from the cell body, project two neurites, one as peripheral fiber and one as central fiber. Visceral afferents participate to visceral sensation and in local reflexes controlling GI functions. Somatic and spinal visceral afferents converging on dorsal horn neurons result in viscerosomatic projection or referred pain.

Cranial Vagal Innervation

Cranial vagal innervation is provided by the vagus nerves which innervate the esophagus, stomach, small intestine, cecum, and proximal colon. Sensory afferent neurons predominate numerically in the vagus nerve. Cell bodies are located in nodose ganglion, and the central processes terminate in the nucleus of the solitary tract (NTS). Vagal afferents are believed as mainly mediating physiological rather than harmful sensations, transmitting information on nature and composition of the intestinal content and motility and contractile tension of the smooth muscle.

Spinal Innervation

Visceral afferents running in the spinal cord are referred as "spinal afferents" when the term "sympathetic innervation" is restricted to spinal efferent innervation [2]. Spinal innervation is provided by greater splanchnic nerve which forms three main ganglia from which they distribute to the viscera: the celiac ganglion

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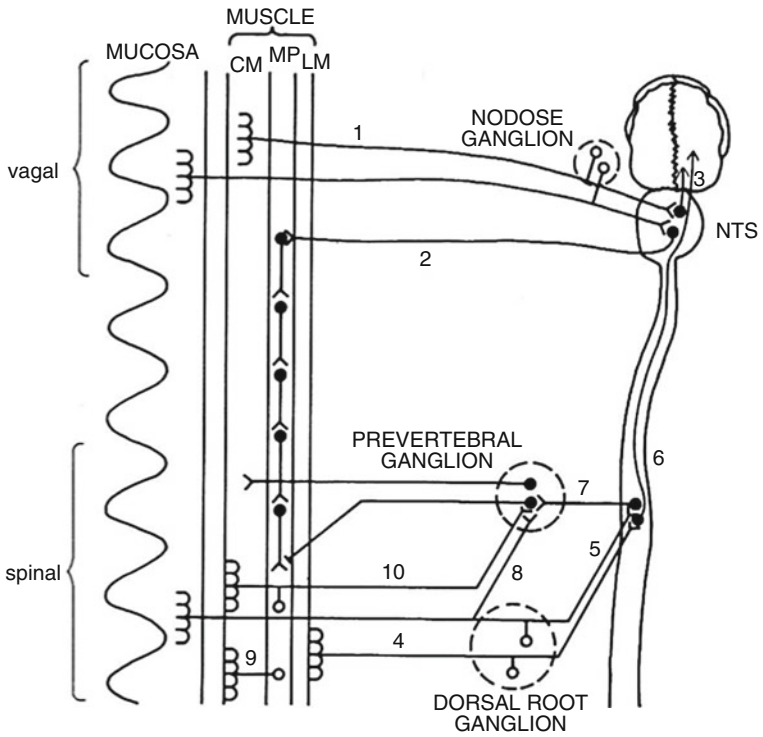

Fig. 4.1 Spinal and vagal innervation of the gastrointestinal tract. *Upper portion*: sensory information from vagal receptors is carried by vagal afferent nerves (*1*) with nerve cell bodies in the nodose ganglion to the sensory nucleus of the solitary tract (NTS). Second-order neurons transmit the information either to higher centers in the CNS (*3*) or via efferent vagal fibers (*2*) in the form of vagovagal reflexes back to the ENS. *Lower portion*: sensory information from spinal receptors located in the mucosa, muscle, or serosa is carried by spinal afferent fibers (*4*) with nerve cell bodies in the dorsal root ganglion to second-order neurons in the spinal cord. Second-order neurons transmit the information either to the CNS (*6*) or via sympathetic nerves (*7*) to prevertebral ganglia, to the ENS, and to the gastrointestinal muscle (spinal reflex). Collaterals of spinal afferents also form short reflex loops with postganglionic sympathetic nerves in the prevertebral ganglion (*8*). In addition to spinal afferents, sensory structures with nerve cell bodies are also located within the intestinal wall (*9*, *10*). *CM* circular muscle layer, *MP* myenteric plexus, *LM* longitudinal muscle layer [139] (Modified from Mayer EA, Raybould HE. Role of visceral afferent mechanisms in functional bowel disorders. Gastroenterology. 1990;99(6):1688–704, with permission)

distributes nerves to the esophagus, stomach, and duodenum; the superior mesenteric ganglion distributes nerves to the intestines down to the ascending colon and the inferior mesenteric ganglion to the colon from the hepatic flexure to the rectum. Sensory afferent neurons account for 10–20 % of fibers in spinal afferents, and cell bodies are located in dorsal root ganglia (DRG) at the cervical, thoracic, and upper lumbar spine [2]. Their central processes terminate in the dorsal horn of the spinal cord. Spinal afferents transmit information on potentially noxious mechanical or chemical stimuli and are involved in sensation of visceral pain [3]. However, it should be kept in mind that, in the CNS, vagal inputs likely integrate with the inputs from the spinal pathways, and therefore, perception of pain is the result of modulation of vagal and spinal inputs [4]. Vagal and spinal afferents are predominantly unmyelinated C-fibers or thinly myelinated A-delta fibers with low conduction velocity.

Sacral Innervation

The distal third of the colon is innervated by pelvic nerves and pudendal nerves. This area of the GI tract receives dual spinal innervation from splanchnic and pelvic afferents [4]. Pelvic spinal afferents connects to the periphery through parasympathetic nerves innervating the pelvic organs. Cell bodies are located in the DRG.

Sensory Terminals

At the level of the gastrointestinal tract, sensory neurons and enteroendocrine cells serve as transducers. Vagal mechanoreceptors are located in the mucosa or muscle layer, and spinal receptors are located in the mucosa, muscle, or serosa [5]. Gut sensory terminals and receptors include mechanoreceptors, chemoreceptors, thermoreceptors, and nociceptors [6]. Recently most evidence points toward polymodality of the visceral receptors.

Vagal Terminals

Vagal sensory endings terminate in the intestinal wall according to different possibilities [5]. “Intramuscular arrays” are located within the circular or longitudinal muscle layers and appear to be stretch receptors. “Intraganglionic endings”

(IGLE) are situated at the surface of myenteric ganglia and are activated by tension of the gut wall. They are supposed to transmit signals that are perceived as nonpainful sensation of fullness. Mucosal projections extend into the lamina propria and correspond to mucosal receptors [7].

Spinal Terminals

Spinal terminals are less well characterized and are anatomically not clearly identifiable. Studies have shown that mechanonociceptors mediating transduction of pain evoked after high amplitude distension are spinal afferents [5]. Fine "varicose branching axons" that appear as specialized endings can be demonstrated in the serosa and mesenteries around blood vessels [7]. Knowledge on mechanotransduction has been recently reviewed [8].

Enteroendocrine Cells

Endoderm-derived enteroendocrine cells are contained in the intestinal mucosa throughout the GI tract behind the esophagogastric junction and provide an interface between external milieu and terminal endings of afferents. They resemble sensory cells in the lingual epithelium taste buds. They have an apical tuft of microvilli exposed to the luminal content and release bioactive molecules (serotonin (5HT)—synthetized by enterochromaffin (EC) cells—and hormones such as CCK, leptin, orexin, ghrelin) that stimulate afferent terminal in the lamina propria in response to appropriate stimuli. Enteroendocrine cells are involved in chemosensitivity and respond to nutrients playing a key role in the glucose homeostasis [9]. It has also been shown that the gut is able to "taste" odorants, spices, and bitter taste via enteroendocrine cells [10]. EC cells contain 5HT that is known to be released in response to endogenous chemical stimuli [11] and exogenous dietary amines, tastants, or microbiota-derived metabolites (e.g., short-chain fatty acids) [12]. They play a key role in the gut mechanosensitivity in response to mucosal deformation: by acting on $5HT_3$ receptors, 5HT release is involved in the peristaltic reflex by activating intrinsic neurons (IPAN) and in visceral sensations by activating mucosal endings of sensory afferents.

Receptors on Visceral Afferents Involved in Visceral Pain

A large number of bioactive substances and chemical mediators have been implicated in the sensory signal transduction of visceral pain. These substances produce their effects by three distinct processes: (1) direct activation of a receptor, which generally involves the opening of ion channels; (2) sensitization, which results in afferent hyperexcitability; and (3) through genetic change that alters the phenotype of the afferent nerve (alterations in the expression or activity of channels and receptors). Figure 4.2 depicts the complexity of receptors and bioactive substances involved in visceral sensitivity in terminal afferents.

Central Pathways of Visceral Sensitivity

Vagal Central Pathway

Vagal afferents project in the brainstem to the NTS which displays a viscerotopic organization [13]. The NTS acts as a relay for the enormous amount of information arriving from abdominal viscera and, in turn, sends out a network to motor nucleus (nucleus ambiguus (NA) and dorsal motor nucleus (DMN)) providing the circuits for basic reflexes of the GI tract. NTS also projects fibers to higher centers: (1) information is relayed to parabrachial nuclei (PBN), which in turn are connected to higher brain centers (amygdala system), and (2) long projections terminate in the thalamus, hypothalamus, and anterior cingulate cortex (ACC) and insular cortical regions regulating arousal, emotional, autonomic, and behavioral responses (see below) [2, 4].

Spinal Central Pathway

After entering the spinal cord, first-order neurons synapse in the dorsal horn and second-order neurons project to the brain through a number of different tracts: spinoreticular, spinomesencephalic, spinohypothalamic (which activate unconscious reflex autonomic responses), and spinothalamic [14]. The spinothalamic tract, the most important pathway involved in conscious sensations, is classically subdivided into lateral spinothalamic tract that mediates the sensory-discriminative aspects of pain (localization, intensity) and medial spinothalamic tract mediating the motivational-affective aspects of pain (suffering, unpleasantness). Lateral spinothalamic tract projects to the ventral posterior lateral nucleus of the sensory thalamus, from which information is relayed to the somatosensory cortex (SI and SII) and the insula cortex. The medial spinothalamic tract projects to medial dorsal and ventral medial posterior nuclei of the thalamus and mainly projects, with spinoreticular, spinomesencephalic, and spinohypothalamic tracts, onto brainstem and midbrain structures such as reticular formation, NTS, periaqueductal gray (PAG), PBN, and hypothalamus. From these structures, third-order neurons project to areas involved in emotional functioning, like anterior the anterior cingulated cortex (ACC) and the orbitomedial prefrontal cortex (PFC). Animal studies have shown that the spinal dorsal column (dorsal funiculus) seems to play also an important role in viscerosensory transmission, especially in nociceptive transmission, but evidence in humans is limited and discussed on the basis of the effectiveness of midline myelotomy in visceral pain due to cancer [15].

Central Processing of Visceral Sensitivity

The main function of somatosensory cortex (SI and SII) is to provide information about intensity and localization of the stimulus (sensory discriminative). The ACC mainly processes pain affect (unpleasantness, pain-related anxiety) and

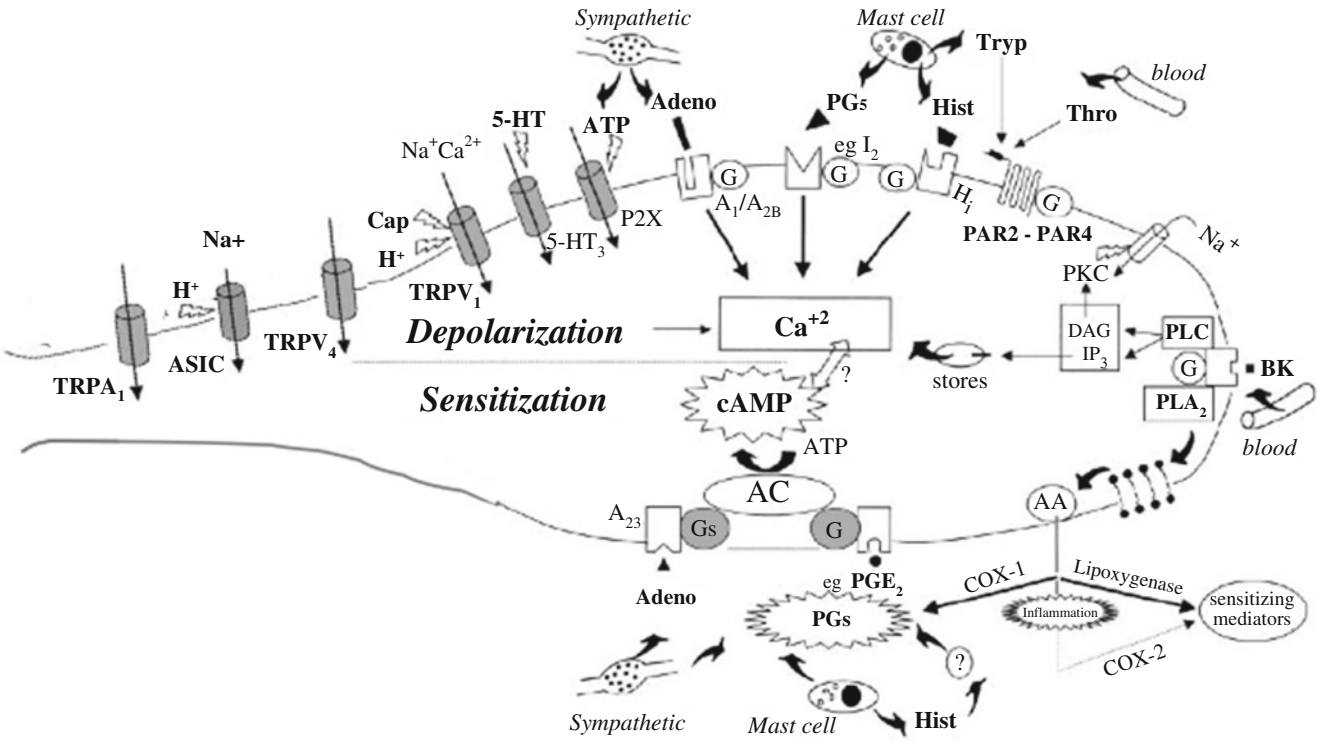

Fig. 4.2 Some of the potential receptor mechanisms underlying activation (depolarization) and sensitization at the terminal of a gastrointestinal sensory afferent [140, 141]. Separate mechanisms underlie activation and sensitization. Some mediators such as serotonin (5HT) cause activation via 5HT3 receptors, whereas others like PGE2 acting at EP2 receptors sensitize visceral afferent responses to other stimuli. Still others, for example, adenosine (Adeno), cause both stimulation and sensitization, possibly through distinct receptor mechanisms. Bradykinin (BK) has a self-sensitizing action, stimulating discharge through activation of phospholipase C (PLC) and enhancing excitability via prostaglandins (PGs) after activation of phospholipase A2 (PLA2). Inflammatory mediators can be released from different cell types (e.g., sympathetic varicosities, mast cells, lymphocytes, and blood vessels) present in or around the afferent nerve terminal. 5HT, ATP, H+, and capsaicin (Cap) can directly activate cation channels such as TRPA1 [142], TRPV1 [90, 91, 142],_ENREF_9 P2X [143], TRPV4 [97, 98], and ASIC [90, 91]. Adenosine, histamine, prostaglandins (not PGE2), and proteases such as mast cell tryptase (Tryp) and thrombin (Thro) act on G protein-coupled receptors (PAR-2 [60] and PAR-4 [86]) leading to a calcium-dependent modulation of ion channel activity. TRPV4 is co-localized with PAR-2 and mainly in colonic sensory neurons with an important interaction in visceral hypersensitivity. Cannabinoids produce peripheral analgesic effect by activation of TRPA1 and indirect activation of TRPV1 [144]. Sensitization, however, may be mediated by increased intracellular cAMP. Adenosine and PGE2 can generate cAMP directly through G protein-coupled stimulation of adenylate cyclase (AC). In contrast, histamine (Hist) may act indirectly through the generation of prostaglandins. The actions of cAMP downstream are currently unknown but may involve modulation of ion channels, interaction with other second messengers (e.g., calcium), or even changes in receptor expression. AA, arachidonic acid; ASIC, acid-sensing ion channels; COX-1 and COX-2, cyclooxygenase-1 and cyclooxygenase-2; DAG, diacylglycerol; IP3, inositol 1,4,5-trisphosphate; PARs, protease-activated receptors; TRPA1, transient receptor potential cation channel A1; TRPV1 and TRPV4, transient receptor potential cation channel subfamily V member 1 and 4 [140] (Modified from Kirkup AJ, Brunsden AM, Grundy D. Receptors and transmission in the brain-gut axis: potential for novel therapies. I. Receptors on visceral afferents. Am J Physiol Gastrointest Liver Physiol. 2001;280(5):G787–94, with permission)

cognitive aspect of the pain experience (attention, anticipation). However, important interactions between these two systems are certainly present. The insula integrates internal state of the organism and encodes sensory and emotional information related to pain. The prefrontal cortex is believed to play a key role in the integration of sensory information and in affective aspect of the sensation. Furthermore, this region is also involved in the generation of and choice between autonomic and behavioral response patterns and has been shown to be a putative biological substrate of cognitive influences (including placebo effect) on emotions and the affective dimension of pain [14]. These brain regions are actually organized and function in complex networks. Schematically, three of them, the salience network, the emotional arousal network, and the sensorimotor network, are involved in chronic visceral pain (for a review, see [16]).

Though a number of analytic techniques and experimental paradigms have been used, quantitative meta-analysis techniques have permitted to pool the results of 18 studies conducted between 2000 and 2010 using PET or fMRI in adult controls and adult IBS subjects undergoing supraliminal rectal distension (painful or not). Data from the healthy

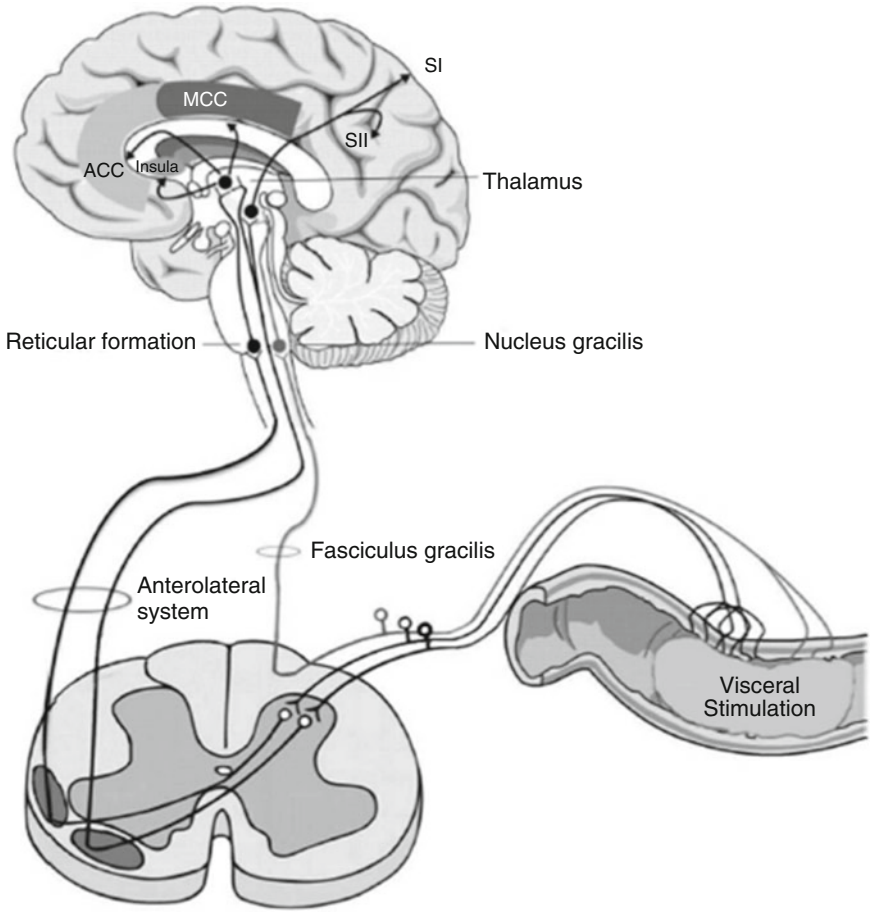

Fig. 4.3 Ascending pathway involved in nociceptive visceral sensation. Colonic stimulation activates afferent spinal terminals whose cell bodies are situated in the dorsal root ganglia. These first-order neurons project to the dorsal horn, and second-order neurons project to the brain through spinoreticular, spinomesencephalic, spinohypothalamic, and spinothalamic tracts. The first three tracts are involved in unconscious reflex behavior, whereas spinothalamic tract drives conscious visceral sensations. Third-order neurons project information to the somatosensory cortex (S1 and S2); to areas involved in emotional functioning, like anterior cingulated cortex (ACC) and the prefrontal cortex (PFC); and to the insula cortex. The spinal dorsal column (dorsal funiculus) seems to play also an important role in viscerosensory transmission, especially in nociceptive transmission

control subjects confirm that regions activated in response to supraliminal rectal distension include zones associated with visceral sensation (bilateral anterior insula, bilateral midcingulate cortex, and right thalamus), emotional arousal (right perigenual ACC), and regions associated with attention and modulation of arousal (left inferior parietal, left lateral, and right medial prefrontal cortex) [17]. There is evidence that the cerebellum is also involved in nociceptive processing and that symptoms of anxiety and depression modulate cerebellar activity during visceral stimulation [18]. Figure 4.3 summarizes the ascending pathway involved in visceral sensation after colonic stimulation.

Descending Modulatory Pathways

Pain afferent stimuli reaching brain structures induce projections able to modulate ongoing transmission of those inputs at the level of the dorsal horn, thus achieving a descending modulatory control. Descending modulation can be inhibitory, facilitatory, or both [2, 14]. At the cortical level, the ACC is the key region involved in this control through projections toward the amygdala and the PAG. Thus, cognitive and affective factors may exert influence on pain transmission through the ACC. The amygdala and the PAG project in turn to the locus coeruleus, the raphe nuclei, and the rostrolateral ventral medulla, which send projections to the dorsal horn and modulate the synaptic transmission of sensory information at this level.

Visceral Hypersensitivity

Definitions applied in visceral sensitivity have been borrowed from the somatic pain field. *Hypersensitivity* is defined as an increased sensation of stimuli (appraised by measurement of threshold volumes or pressure for first sensation or pain). *Hyperalgesia* is an increased pain sensation to a certain painful stimulus and *allodynia* a stimulus previously not perceived as being painful that becomes painful. Visceral hypersensitivity is defined as an exaggerated perceptual response (hyperalgesia, allodynia, abnormal somatic referral) reported to peripheral events. Theoretically, visceral hypersensitivity could be the result of changes in visceral afferent signal processing (reflecting increased visceral afferent input to the brain from the gut) or be the consequence of alterations in pain modulation mechanisms (i.e., central sensitization or pain inhibition process at the level of

the central nervous system), or be due to alteration of pain processing or derive from a variable combinations of these pathways.

In pediatrics, several independent groups have reported that 75–100 % of children affected by IBS have a low rectal sensory threshold for pain (i.e., visceral hypersensitivity) as compared to control children [19–23]. In adults, the prevalence of visceral hypersensitivity varies from 20 % [24] to 94 % [25] across studies suggesting that visceral hypersensitivity is a more reliable diagnostic marker in children than in adults.

Aberrant viscerosomatic projections have also been reported in children with IBS and FAP who refer, in response to rectal distension, their sensation to aberrant sites compared to the controls, i.e., with abdominal projections on dermatomes T8 to L1 wherein controls referred their sensation to the S3 dermatome. In adults and in children, visceral hypersensitivity has been shown to be "organ specific" with a low rectal sensitivity threshold in IBS patients [25–32], a low gastric sensitivity threshold in FD [33–36], and "diffuse" hypersensitivity in mixed IBS + FD patients [37].

Data from studies on the visceral hypersensitivity in FGID and specifically in IBS favor the heterogeneity of causes and mechanisms in a population of patients. Preclinical animal models have permitted investigations of cellular and molecular abnormalities in the gastrointestinal tract as well as in the CNS (spinal cord and brain) [38, 39]. In humans, studies have similarly found several modifications in the rectal and colonic mucosa (inflammation, mast cell infiltration, serotonin pathway anomalies) in IBS patients. On the other hand, functional brain imaging techniques have demonstrated, in adults and in adolescents, the importance of a role for CNS dysregulation of pain processing in IBS.

Peripheral Mechanisms

Inflammation and Epithelial Permeability

It is clearly accepted that IBS may be triggered by enteric bacterial infections that could have consequences on local inflammation, EC cell, and mast cell counts [40, 41]. Low-grade inflammation has been reported in the enteric ganglia [42] and in the mucosa [42, 43] of patients with IBS. A slight increase of fecal calprotectin is reported in children with IBS [44]. Proinflammatory cytokine (IL-1, IL-6, and TNF-α) production by peripheral blood mononuclear cells is upregulated in patients with IBS [45]. This suggests that inflammatory status drives possibly local modifications promoting sensitization. Stress via the hypothalamic-pituitary-adrenal (HPA) axis modulates the inflammation and the cytokine production. Increased intestinal permeability either jejunal or colonic [44, 46] with alterations of the junction protein expression [47, 48] is also associated to the minimal mucosal inflammation.

Mast Cells and Mucosal Innervation

Abnormal mast cell numbers (increase [49–51] or decrease [52]) and close proximity to mucosal enteric neurites has been reported in stressed rats [49, 50] and in the colon of adult [51, 52] as well as pediatric [53, 54] patients with IBS (for a review, see [55]). Stress-related activation of the HPA axis increases mast cell number and triggers mast cell degranulation via the corticotropin-releasing factor (CRF). Triggers of mast cell degranulation include also IgE, histamine, substance P, calcitonin-related gene peptide, nerve growth factor (NGF), and lipopolysaccharide. Current evidence suggests that activity and enhanced degranulation of mast cells rather than an increased number is predominant in the pathophysiology of visceral hypersensitivity.

CRF, released by the paraventricular nucleus of the hypothalamus, by activating CRF1 receptor either in the brain or in the colonic mucosa, plays an important role in modulating the water and ion secretion, colonic motility, and intestinal permeability via nerve-mast cell interaction as well as directly on intestinal epithelium (for a review, see [56]).

NGF [54, 57, 58], tryptase [59, 60], and histamine are mediators released by mast cells that activate afferent nerves and might therefore mediate the visceral hypersensitivity [59]. NGF evokes nerve fiber growth and pain transmission by interaction with the tyrosine kinase receptor A (TrkA). Dothel et al. have shown that patients with IBS have a higher density of mucosal nerve fibers and increased nerve outgrowth in the colonic mucosa. These findings were associated with increased expression of NGF and TrkA, both expressed on the surface of mast cells [61]. Willot et al. reported a higher NGF content in colonic biopsies from children with diarrhea-predominant IBS [54].

Enteric Glial Cells

Enteric glial cells (EGC) are a major component of the enteric nervous system with an extensive network throughout the intestinal mucosa. They play an important role in the control of intestinal motility and are involved in intestinal epithelial barrier function to maintain intestinal homeostasis and in repair mechanism after mechanical or inflammatory injury. In physiological conditions, EGC can be activated by bacteria, luminal factors, or neuronal factors. EGC-derived factors such as S-nitrosoglutathione, GDNF, and TGF-β are important mediators by reducing epithelial permeability

[62–64]. A recent study demonstrated the association of EGC activation and stress-induced colonic hypercontractility in an IBS-mouse model [65].

Serotonin Pathway

Serotonin (5HT) is secreted by enterochromaffin (EC) cells and plays a critical role in the regulation of GI motility, secretion, and sensation through specific receptors [66–70]. The subtypes $5HT_3$, $5HT_4$, and $5HT_{2B}$ are supposed to be the main receptors involved in visceral sensitivity [71]. 5HT synthesis and bioavailability are also under dependence of the microbiota [72, 73]. The 5HT transporter (SERT) terminates the actions of 5HT by removing it from the interstitial space [74–76]. Genetic polymorphism of SERT could influence visceral sensitivity: the short allele of the gene 5HTTLPR is associated with reduced 5HT transporter (SLC6A4) function and higher rating of rectal pain sensation and altered brain activation [77]. Coates et al. have reported that mucosal 5HT, tryptophan hydroxylase-1 messenger RNA (TpH1, the rate-limiting enzyme in the biosynthesis of 5HT), and SERT mRNA were all significantly reduced in colonic mucosa of adult patients with IBS [78]. In children, 5HT content was found significantly higher in the rectal mucosa of pediatric subjects with IBS as compared to controls, and SERT mRNA was significantly lower in patients than in controls [79]. Park et al. have shown a correlation between EC cells and rectal hypersensitivity in adults suggesting that these cells play a role in visceral sensitivity [80].

PAR-2 and PAR-4

Protease-activated receptors (PAR) are G protein-coupled receptors that are activated after cleavage by proteases of their N-terminal domain, which releases a tethered ligand that binds and activates the receptor. PARs can be activated by mast cell tryptase, pancreatic trypsin, and exogenous proteinases [81]. PAR-1, PAR-2, and PAR-4 are distributed throughout the GI tract. PAR-1 and PAR-2 are involved in modulation of intestinal inflammation [82, 83], and PAR-2 [84] and PAR-4 are key players in visceral pain and hypersensitivity. Activation of PAR-2 is pronociceptive [60, 85], and PAR-4 is conversely an inhibitor of visceral hypersensitivity [86, 87]. It is conceivable that visceral hypersensitivity may result from disequilibrium between the pronociceptive effects of PAR-2 activation (or overexpression) incorrectly counterbalanced by the antinociceptive effect of PAR-4 activation (or low expression).

TRPV1, TRPV4, and TRPA1

Members of the transient receptor potential (TRP) family of ion channels are important sensors of environmental stimuli [88, 89]. TRP vanilloid 1 (TRPV1) ion channel is expressed in primary afferent neurons. A role of TRPV1 in visceral hypersensitivity is supported by several studies in rodents showing that TRPV1 mediates visceral nociception behavior [90–92]. In human adults, a potential role of TRPV1 is supported by a higher density of TRPV1 fibers in the colonic mucosa of patients with IBS as compared to controls [93] but not confirmed by others [94]. Rectal application of the TRPV1-agonist capsaicin results in increased pain response in IBS patients [94]. Sugiuar et al. have shown that TRPV1 function is enhanced by 5HT in colonic sensory neurons [95]. Such mechanism involving histamine H1 receptors was recently demonstrated in humans [96]. Therefore, sensitization rather than overexpression of TRPV1 is hypothesized to explain hypersensitivity. Studies have also emphasized the role of TRPV4 expression and function in visceral nociception [97–99]. TRPV4 is expressed in visceral afferent neurons [98] and epithelial colonic cells [97]. TRPV4 is responsible for 5HT and histamine-induced visceral hypersensitivity [100] and is thought to be the mediator of PAR-2-induced colonic sensitization [97, 99].

TRPA1 is present in colonic myenteric neurons, but also in numerous non-neuronal tissues, including the colon [101]. Cold and mechanical stimuli but also products formed during oxidative stress can activate TRPA1. Activation of TRPA1 results in mechanical hypersensitivity. Cenac et al. have evaluated levels of metabolites that activate calcium channels TRPV1, TRPV4, and TRPA1 in IBS patients. The level of the TRPV4 agonist was elevated, but not the levels of the other agonists [102]. Figure 4.4 summarizes the complex interactions among the different factors responsible for visceral hypersensitivity involved at the peripheral level.

Central Mechanisms

When measured by using rectal distensions in humans, the perceptual response expressed by the subject and measured as the rectal sensory threshold can be separated into two components according to the signal detection theory [103–105]: the *perceptual sensitivity* (the physiological capacity of the neurosensory apparatus of the rectum to detect intraluminal distension, i.e., the ability to detect intraluminal distension) and the *response bias* (how the sensation is reported). The *perceptual sensitivity* reflects the ability of the organ to detect and transduce the stimulus to the central nervous system. The *response bias* is the reporting behavior (intensity, painfulness) which represents a cognitive process influenced by past experience and psychological state. Increased response bias (i.e., a tendency to report as painful visceral sensations)

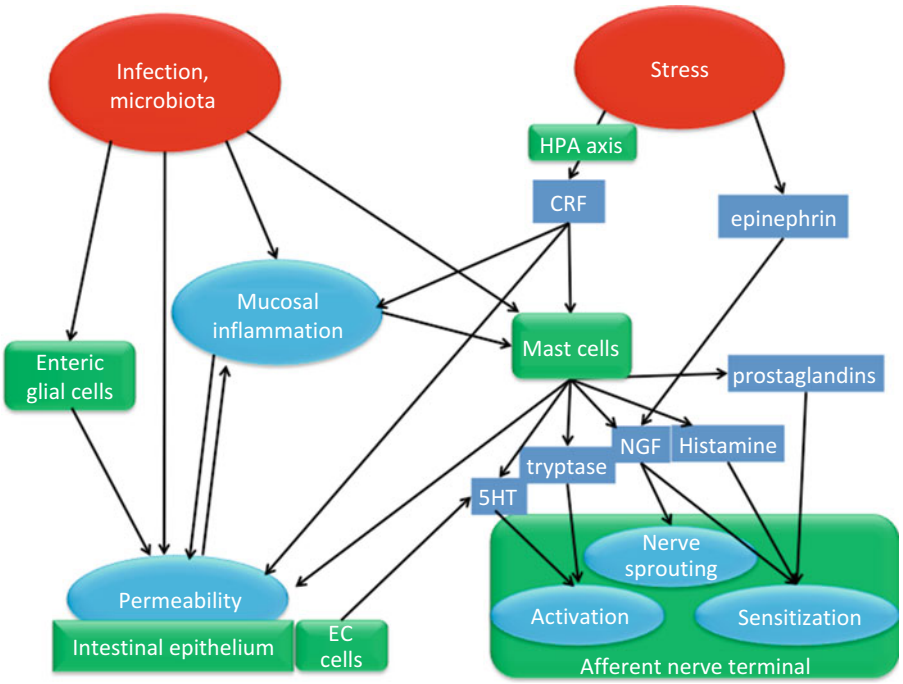

Fig. 4.4 Pathophysiology of visceral hypersensitivity: peripheral mechanisms. Enteric infection, dysbiosis, or stressful events activate intestinal epithelium, enterochromaffin (EC) cells, enteric glial cells, mast cells, and afferent nerve terminals. Physiological events such as mucosal inflammation and increased intestinal permeability as well as CRF and epinephrine secretion elicit mast cell degranulation and EC cell stimulation which in turn secrete neurotransmitters (5HT, histamine), neurotrophins (NGF), proteases, and prostaglandins. These bioactive substances activate receptors present at the terminal end of the afferent nerves and elicit pain, sensitization, and neurite outgrowth leading to chronic changes and maintenance of chronic pain. *Red*: trigger events eliciting visceral hypersensitivity; *green*: tissues involved in visceral hypersensitivity; *light blue*: pathophysiological mechanisms responsible for visceral hypersensitivity; *dark blue*: some of the bioactive substances activating receptors at the terminal end of afferent spinal neuron. Note that some of these components may stimulate mast cell degranulation therefore creating a loop with amplification of the nerve activation. *CRF* corticotropin-releasing factor, *NGF* nerve growth factor, *5HT* serotonin, *EC cells* enterochromaffin cells

with a similar perceptual sensitivity than controls (i.e., same ability as controls to discriminate rectal distensions) has been reported by one group [106] but was not confirmed by others [107].

Though perceptual sensitivity can be related to peripheral mechanisms, response bias results of central modulation of the stimuli, and processing of the sensation.

Central Sensitization and Altered Brain-Gut Communication

Central sensitization is a phenomenon that has been described in chronic somatic pain [108, 109]: a peripheral injury triggers a long-lasting increase in the excitability of spinal cord neurons inducing an increase in the afferent activity secondary to profound changes in the gain of the somatosensory system. This central facilitation results in allodynia, hyperalgesia, and a receptive field expansion that enables input from non-injured tissue to produce pain (secondary hyperalgesia). In an animal model of stress-induced visceral hyperalgesia, spinal microglia activation has been shown to play a key role in facilitation of pain stimuli [110]. In a stressful model of visceral hypersensitivity, increased colonic NGF synthesis in response to epinephrine has been shown to be responsible for the central sensitization [111]. In humans, using RIII reflex, evidence of an alteration (facilitation) of spinal modulation of nociceptive processing has been shown in IBS [112]. Stabell et al. investigated pain thresholds in 961 adolescents in the general population. Adolescents with IBS symptoms had lower pain thresholds with widespread hyperalgesia. The association of visceral hypersensitivity to somatic thermal hyperalgesia has also been reported by some authors in a subset of IBS adult patients [30, 113, 114]. These findings are supporting the theory of central sensitization mechanism

[115]. Alterations of pain inhibition processes in adult [114] as well as young girls [116] with IBS have also been reported.

Dysregulation of Pain Processing

Functional cerebral imaging techniques have led to significant progress in the understanding of cortical and subcortical processing of pain in IBS. The results of the previously cited meta-analysis of 18 studies performed in adult controls and IBS subjects undergoing supraliminal rectal distension (painful or not) support a role for CNS dysregulation of pain processing in IBS [17]. Visceral pain processing is a complex process and results from interactions of brain areas operating in networks (the salience network, the emotional arousal network, and the sensorimotor network). Structural and functional alterations in those brain regions as well as prefrontal regions are the most consistently reported findings in adult IBS as compared to controls [16]. A recent study in adolescent patients with IBS demonstrated also a greater extent and magnitude of activation to rectal distension than healthy controls in a number of key areas of the salience network, especially the cingulate and insular cortices that are involved in visceral afferent and emotional arousal processing [117].

Other Potential Mechanisms

Other neuromediators involved in visceral sensation that have been studied as potential peripheral or central mechanisms of visceral hypersensitivity are listed below. Some of them are (or have been) actively studied as possible targets for treatments of FGID.

- Glucocorticoid receptor [118]
- Neurokinins which include the substance P (SP), neurokinin A, and neurokinin B and their respective neurokinin receptors NK1R, NK2R, and NK3R [119]
- Cannabinoids [120] and cannabinoid receptor-1 which regulate intestinal barrier [121]
- Opioids [122]
- GABA [123]
- Glutamate (and ionotropic and metabotropic receptors) [124]
- Voltage-gated sodium channels [125]
- Carbon monoxide and hydrogen sulfide [126]
- NaV 1.9 [127]

Visceral Hypersensitivity: A Pediatric Perspective

Although visceral hypersensitivity has been demonstrated in children and adolescents with abdominal pain related to FGID, most studies have been conducted in adults for whom the duration of symptoms is significantly longer than pediatric patients precluding the possibility of uncovering the initial pathophysiological mechanisms. Besides the previously discussed peripheral and central mechanisms associated to visceral hypersensitivity, numerous other factors specific to a child with functional abdominal pain, such as age of the child, genetic background, temperament and psychological traits, previous exposure to painful stimuli, parental beliefs, and psychological traits as well as parental interaction with the child, may lessen or exacerbate the symptoms and the chronicity of symptoms.

Furthermore, it is well known that maturation of pain perception is a dynamic process along child's development starting during fetal life and ending throughout adolescence [128]. Regarding visceral pain, there is a paucity of data in this respect although the development and maturing of the enteric nervous system is well described. The maturation of the interactions between the ENS and the central nervous system and the formation of the brain-gut axis are largely unknown. Studies done in rodents indicate that the neonatal period is characterized by a very high susceptibility to stress leading to visceral hypersensitivity in adulthood. Neonatal colonic [129] or gastric [130] irritation, maternal deprivation [131], and gastric suctioning [132] have been shown to induce visceral (colonic [129, 131, 132] or gastric [130]) hypersensitivity in animal models.

In humans, studies on somatic pain have shown that early traumatic and painful experiences can induce long-term alterations in sensory and pain processing in children [133, 134]. Some studies have also shown that surgical procedures in infants may lead to chronic abdominal pain [135], and, though different from neonatal stress, childhood trauma and abuse are strongly associated to IBS in adults [136].

However, since visceral sensitivity processing is highly complex with involvement of peripheral and central nervous systems influenced by cognitive and psychological processes, not all infants who experience early trauma will develop functional pain. Individual differences among babies as well as parental attitude, parental psychological traits, and parental beliefs may amplify or dampen their response to these events associated with increased pain reactivity later in childhood. In keeping with this idea, it has been shown that response to pain in school-aged children with previous experience in a NICU is highly influenced by the mother's behavior [137, 138].

Figure 4.5 depicts a schematic overview of the complex interactions between a child, his/her parents, and the environment leading to visceral hypersensitivity and chronic visceral pain.

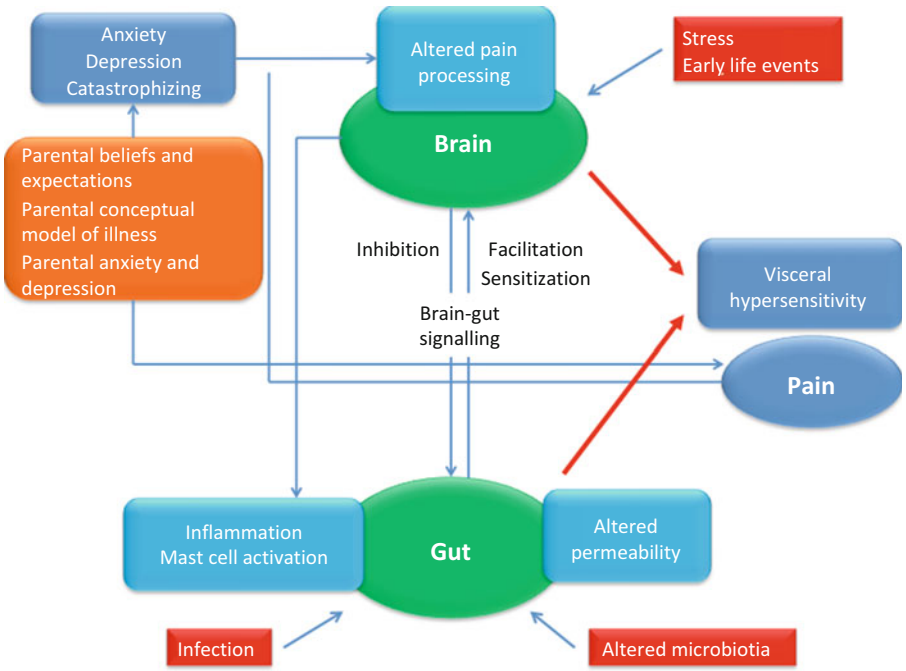

Fig. 4.5 Conceptual framework of visceral hypersensitivity in children. Enteric infection or dysbiosis activates intestinal epithelium and promotes inflammation, mast cell activation, and increased intestinal permeability leading to sensitization of afferent nerves and visceral hypersensitivity. Activation of the gut-brain axis with possible central sensitization and abnormal descending inhibition or increased facilitation can alter the central pain processing and generate visceral hypersensitivity. Stressful events, either in the neonatal period or later in life, induce an activation of the hypothalamic-pituitary-adrenal axis which promotes peripheral mast cell activation and inflammation favoring peripheral visceral hypersensitivity. Stress may also alter the central pain processing and brain-gut axis leading also to abnormal visceral sensitivity. Pain, especially in the context of parental catastrophizing or misunderstanding of the situation, can trigger anxiety and depression in the child which in turn will increase stress and alteration of pain processing leading to a vicious circle with an amplification loop conducting to a chronic pain. *Red*: trigger events eliciting visceral hypersensitivity; *dark blue*: child-related specific characteristics; *green*: organs involved in visceral hypersensitivity; *light blue*: pathophysiological mechanisms responsible for visceral hypersensitivity; *orange*: factors associated to the child's parents

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The Microbiome in Neurogastroenterology

5

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The human gastrointestinal (GI) tract harbors a rich and diverse community of organisms referred to as the microbiota. The microbiota contains an even more complex sum of genetic material. This microbiome (gut microbes and their gene repertoires) contributes to a wide variety of functions critical for intestinal and host health including nutrient assimilation and metabolism, pathogen resistance, immunoregulation, and modulation of intestinal secretion and motility [1–3]. Gut microbes only recently have been acknowledged as integral components within the biopsychosocial model of functional GI disorders (FGIDs). Microbes are required for normal development and regulation of the enteric nervous system (ENS) and central nervous system (CNS); by circulating messages through host cellular mediators, microbes are essential to the bidirectional communication along the brain-gut axis.

This bidirectional communication occurs through the complex interactions of host gene expression, environmental stimuli, and microbial metabolite production orchestrating a myriad of processes including gut motility, sensation, intestinal barrier function (permeability), immunity, mucosal inflammation, hunger, stress, and emotion. Underlying each of these processes, microbial-derived signals pass between epithelial, enteroendocrine, immune, muscle, and nerve cells via receptor-mediated signaling pathways. In turn, the richness and diversity inherent to intestinal microbial ecosystems may be altered by stress, environmental stimuli, introduction of new species (probiotics), substrate availability (diet or prebiotics), or antibiotic compounds.

This chapter outlines the role that intestinal bacteria play in regulating the sensorimotor functions of the GI tract and reviews the current evidence for microbiome-based therapies that seek to improve human health in FGIDs. These interventions include probiotics, live microorganisms that when consumed in adequate amounts confer a specific health benefit on the host [4]; prebiotics, nondigestible dietary components that improve host health by selectively enhancing beneficial populations or functions of select components of the microbiota [5]; and targeted antibiotics. The means by which gut microbes affect intestinal barrier function, ion secretion, and immunity are beyond the scope of this chapter and recently have been reviewed elsewhere [6, 7].

A Historical Perspective: The Early Years of the Microbiome and Neurogastroenterology

Gut bacteria became inextricably linked to the field of neurogastroenterology in the mid-twentieth century following the development of the first germfree animal facility at the University of Notre Dame. Early observations revealed a costly and surprisingly prevalent morbidity among germfree livestock: intestinal volvulus due to massive cecal enlargement. In 1959, Wostmann and Bruckner-Kardoss challenged the prevailing theory that a nutritional deficiency in the sterilized diet caused the cecum to enlarge. Rather, they suggested, "The absence of certain stimuli, normally arising from the presence of the microbial flora and/or its metabolic activity, in these animals appears to be the prime etiological factor" [8]. This hypothesis was confirmed by studies showing amelioration of cecal enlargement with introduction of microbes [9] and by reproduction of cecal enlargement in conventionally raised mice following antibiotic treatment [10]. Immunohistochemistry revealed an architecturally abnormal myenteric plexus containing enlarged and metabolically inactive neurons [11], and ex vivo organ cultures revealed decreased spontaneous contractile activity and blunted neurotransmitter-induced excitability in the germfree cecum [12].

In 1966, Abrams and Bishop sought to explain their observation that the infectious burden of *Salmonella*

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typhimurium was several orders of magnitude higher in germfree compared to conventionally raised mice [13]. Hypothesizing that delayed GI transit in germfree animals provided pathogens with additional replication time, the authors revealed markedly delayed transit in germfree mice [13, 14]. Mathias et al. used another infection model in 1976, cholera injection into the rabbit ileal loop, to record for the first time an organized migrating motor complex (MMC) using surgically implanted electrodes. This system prompted the discovery that cholera toxin alters not only small intestinal secretory but also motor patterns [15]. Shortly thereafter, interdigestive MMCs were discovered in humans [16]. Disruption of these "housekeeping" MMCs was associated with small bowel bacterial overgrowth (SBBO) measured by $^{14}CO_2$ bile acid breath test [16], and SBBO was reproduced in rat models by disrupting the MMCs either medically [17] or surgically [18, 19]. Germfree animals exhibited delayed MMC periodicity, which was corrected by reintroducing microbes to the system [20, 21].

The work by these pioneers led to deeper investigations using the technologies of today. Global transcriptome profiling studies have begun to lend insight into molecular mechanisms underlying the physiologic changes observed in germfree intestines, implicating altered expression of host genes contributing to smooth muscle protein and neurotransmitter function [22]. However, not all bacteria influence contractile patterns and motility equally [23], and the development of culture-independent next-generation sequencing technologies that ushered in the 2007 launch of the Human Microbiome Project [24, 25] provided new opportunities to define previously undetectable species and to measure entire microbial populations simultaneously. High-throughput pyrosequencing of bacterial 16S ribosomal DNA now permits rapid, low-cost microbial population surveys, while newer technologies including whole metagenomic sequencing of all microbial genes [26] and metabolomics, the measurement of microbial- and host-derived small-molecule metabolites by mass spectrometry-based approaches, have begun to lend insight into the functional contributions of gut microbes to the field of neurogastroenterology.

The Intestinal Microbiome: Development and Anatomy

The intestinal microbiome matures with age and concomitant dietary exposures, gaining richness and diversity over time. Infants are not born with a complex, adult-like microbial community; rather, bacteria colonize healthy newborns in a predictable sequence known as *succession* [27]. The notion that healthy infant guts are first seeded by microbes during passage through the birth canal and early breastfeeding has recently been challenged by the suggestion that normal microbial colonization may begin in utero [28, 29]. During the neonatal period, the structure and function of intestinal microbial communities are heavily influenced by components of breast milk and glycan constituents of intestinal mucus [30]. General patterns of succession are predictable, although variations exist based on multiple factors including mode of delivery, antibiotic use, maternal contact, and early nutrition [31, 32], gender [33], and diet or geographic region [34–36]. The microbiota of most healthy children converge upon a more complex, adult-like community that is thought to be stable [37, 38] and thus more resilient from disturbances that threaten host health. Initially the maturation process was thought to be completed between the introduction of solid foods and 3 years of life [32, 35, 39]; however, recent studies show that subtle differences remain between adults and children up to age 4 [40], preadolescents up to age 7 to 12 years [41], and young adults up to age 11 to 18 years [42].

The microbiome forms environmental niches within each individual, assembling in a nonrandom topography that ultimately benefits both host and microbe [43]. Microbial communities differ not only based on their longitudinal position from the proximal to distal GI tract [33, 44, 45] but also according to their position along the cross-sectional axis, from the lumen to the mucosa. One study evaluating patients newly diagnosed with inflammatory bowel disease and healthy controls found that site of sample origin (colonoscopic mucosal biopsy vs. feces) was more important as a determinant of microbiota composition than whether a subject was healthy or had active disease [46]. This distinction between mucosal and fecal microbiota is especially important for neurogastroenterology. Given that the ENS with its thousands of ganglia and 400 million neurons embedded within the GI mucosal wall is in closest proximity to the mucosal—not luminal—microbiota, mucosal organisms are thought to influence ENS function more profoundly than fecal microbiota that transiently pass through the intestine. The majority of published human studies describe the fecal microbiota exclusively, and these results must be interpreted with caution. However, it also should be noted that surgical or endoscopic mucosal samples are difficult to obtain, especially from healthy controls. Furthermore, the microbial composition of these samples is heavily influenced by standard preprocedure bowel preparation [47].

Mechanisms of Microbial Influence on the Gut-Brain Axis: Enteric Nervous System Developmental Considerations

Despite the discovery decades ago that gut bacteria influence intestinal sensorimotor function, the majority of mechanisms by which the microbiota communicates with the host ner-

vous systems remain largely uncharacterized. Most studies in this area have sought to elucidate how intestinal bacteria modulate established sensorimotor pathways in adults. Surprisingly little is known regarding how microbes affect the establishment of these neural circuits in early development.

Microbes play important roles in ENS and intestinal epithelial cell lining development. Since Dupont's early observation that rats born in the germfree state develop a hypoplastic and hypofunctioning myenteric plexus [11], further evidence indicates that microbes are essential for normal development of the ENS and motor circuits. Germfree rats have altered crypt-villus and mucosal architecture, with abnormal distributions of enteroendocrine cells secreting the motility-regulating hormones gastrin, serotonin, and motilin [48]. Germfree mice exhibit ENS abnormalities including decreased density of neurons and altered nitrergic expression as early as day-of-life three; these findings correlate with decreased amplitude and frequency of intestinal smooth muscle contractions [49]. However, normal ENS development does not require a completely intact microbiota given that gnotobiotic (animals with known selective strains of microbiota present) mice colonized by a defined minimal microbial population have normal motor function [49]. Some developmental effects may be mediated by specific microbes, not just the presence or absence of all bacteria. For example, in neonatal piglets with normal microbiota, supplementation with the probiotic *Pediococcus acidilactici* alters intestinal architecture [50] as well as enteric neuronal distribution and activity [51]. Further characterization of ENS developmental effects by the microbiota and the mechanisms that govern these changes are avenues of active study.

Mechanisms of Cross Talk Between Microbe and Host That Influence Intestinal Motor Patterns

Microbial Factors

Mechanisms by which microbes influence intestinal motor patterns have been explored using germfree, gnotobiotic, and probiotic-supplemented animals. Evaluation methods include in vivo imaging, tracking the movement of a nonabsorbable liquid marker to measure transit time, assessing expulsion of a bead after rectal insertion to determine rectosigmoid motility, implanting surgical myoelectric recording devices or catheters for site-specific measurements of transit time or luminal content or for pharmacotherapy administration, and creating ex vivo organ bath systems that facilitate myoelectric measurements. In some cases, specific microbial-derived molecules that influence motility have been identified, which likely diffuse through the mucus layer to activate receptors on enterocytes or enteric nerves (Fig. 5.1). At this time, the mechanisms underlying microbial-host signaling remain largely uncharacterized. Here we will review the current knowledge of enterotoxins, neurotransmitter analogues, and other microbial-derived molecules that influence motility.

Bacterial toxins mediate a wide range of effects on motility through different cells, receptors, and mechanisms. Early studies with purified cholera toxin [15] and conditioned media from either toxigenic *Escherichia coli* [52] or *Clostridium difficile* [53] provided direct evidence that bacterial secretion products can enhance intestinal myoelectric activity and accelerate transit. However, not all toxins function similarly. *C. difficile* toxin A inhibits small bowel motility [54] and evokes capsaicin-sensitive afferent neuron and immune cell responses [55]. Cholera toxin excites multiple contractile circuits, affecting propulsive and segmentation reflexes via separate pathways [56].

Bacterial cell wall components, which may be toxic, may also affect motility. In a rat model of endotoxemia-induced dysmotility, intravenous administration of *E. coli*-derived lipopolysaccharide (LPS) increases activity of nitric oxide synthase, delays gastric emptying, and accelerates small bowel transit [57]. An elegant set of studies evaluated germfree mice, mice with antibiotic-depleted microbiota, and mice lacking components of LPS receptor signaling (toll-like receptor 4 or its adaptor protein Myd88). Each of these three "LPS-deficient" animal models exhibited delayed intestinal motility and reduced numbers of nitrergic neurons. LPS was also shown to increase survival of neuronal cells in what appears to be a nuclear factor-KB (NF-KB)-dependent mechanism [58]. In a separate model, intraperitoneal administration of LPS induced nuclear translocation of NF-KB in mouse intestinal smooth muscle and myenteric plexus cells [59]. Furthermore, recent studies suggest that LPS induces muscularis macrophages to increase their expression of bone morphogenic protein 2, which in turn influences motility via receptors on enteric neurons in a pSMAD-dependent fashion [60].

Microbiota-produced nontoxic compounds also affect host motility. It has been known for decades that some unicellular organisms produce biologically active hormones [61]. For example, *Bacillus subtilis* synthesizes a bioactive somatostatin-like molecule [62], and multiple pathogenic bacteria produce γ-aminobutyric acid (GABA) [63]. Gnotobiotic mice "humanized" by colonization with a simplified human-derived microbiota then given either *Lactobacillus paracasei* or *Lactobacillus rhamnosus* had elevated urine concentrations of the metabolite tryptamine [64]. Tryptamine is an aromatic amino acid compound that enhances intestinal contractility in ex vivo preparations and stimulates the release of other neurotransmitters [65]. *Clostridium sporogenes* was recently discovered to have a

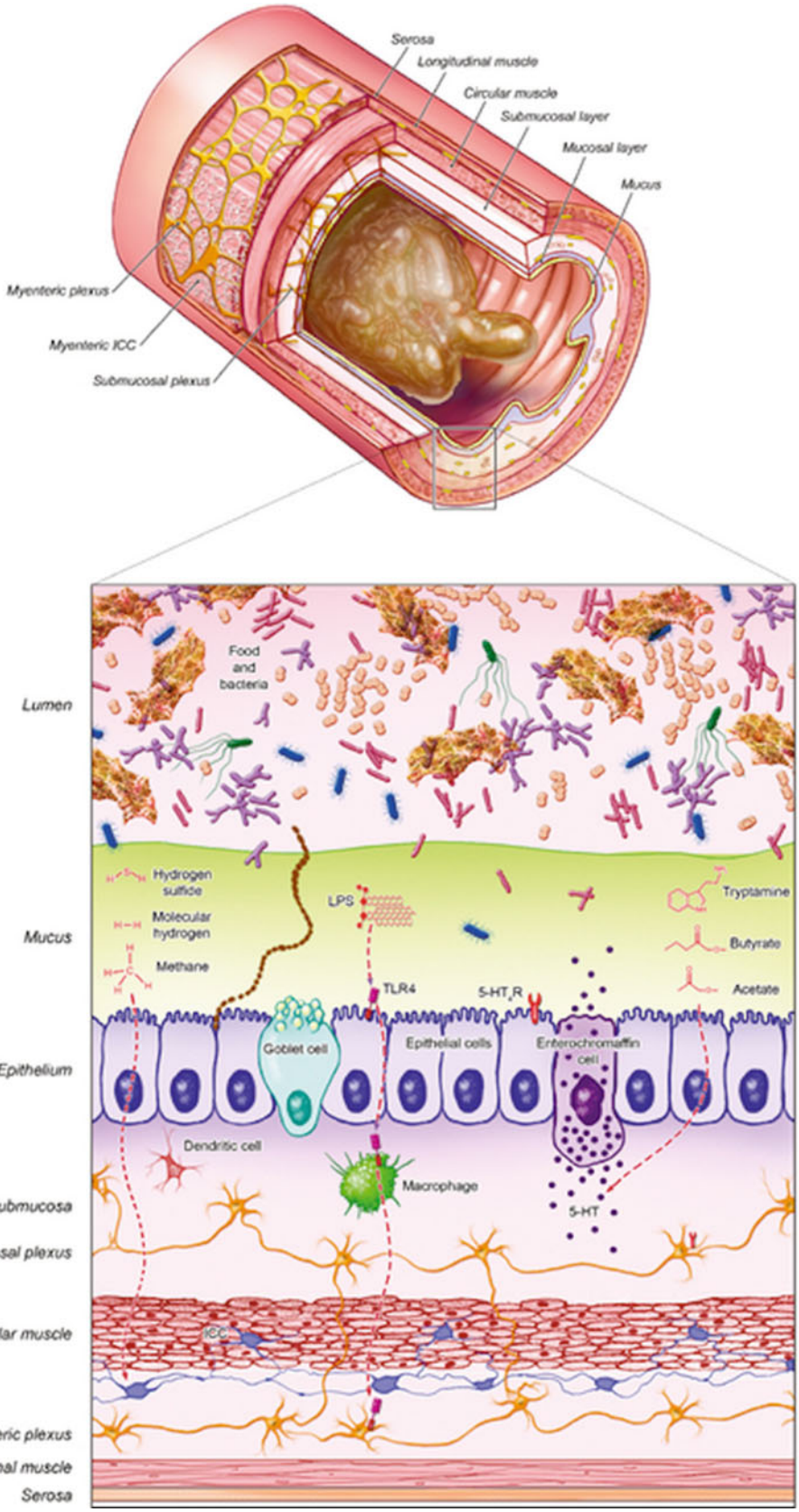

Fig. 5.1 Structural relationship between the luminal and mucosal microbiota and the enteric nervous system (From Reigstad CS, Kashyap PC. Beyond phylotyping: understanding the impact of gut microbiota on host biology. Neurogastroenterol Motil. 2013;25(5):358–72, with permission)

tryptophan decarboxylase enzyme capable of synthesizing the neurotransmitter tyramine. Microbial tyramine synthesis is now believed to be present in the intestinal tracts of more than 10 % of the human population [66]. Other studies have linked gut bacteria to increased levels of the enteric gaseous neurotransmitters hydrogen sulfide [67] and nitric oxide [68, 69].

Microbes also can receive signals from the host neurobiological environment. Quorum sensing is the microbial regulation of gene expression in response to fluctuations in cell population density [70]. Quorum sensing could provide an evolutionary explanation for the presence of a GABA uptake system in a *Pseudomonas* species [71], if this system evolved to detect the density of other GABA-producing bacteria. However, bacterial functions are likely influenced by differing concentrations of GABA derived from the host as well. In turn, there are multiple examples of human catecholamines that influence a range of bacterial processes including growth, attachment, and virulence [72] (Fig. 5.2).

Short chain fatty acids (SCFAs), which are fermentation products that fuel intestinal epithelial cells in a site-specific and dose-dependent manner [73], are the most extensively studied class of microbial-derived molecules that influence host motility. Since the discovery that intraluminal infusion of SCFAs stimulates local motility in the human distal intestine [74], key mechanistic insights have been revealed using in vivo and ex vivo models from rat [75–79] and guinea pig [80]. One potential mechanism by which SCFAs affect motility is by increasing choline acetyltransferase activity in myenteric neurons through a monocarboxylate transporter 2-dependent mechanism. Altered choline acetyltransferase activity was found in rats given either butyrate or a resistant starch diet [81]; the resistant starch may act as a prebiotic to increase the numbers or activity of butyrate-producing microbes in the intestine.

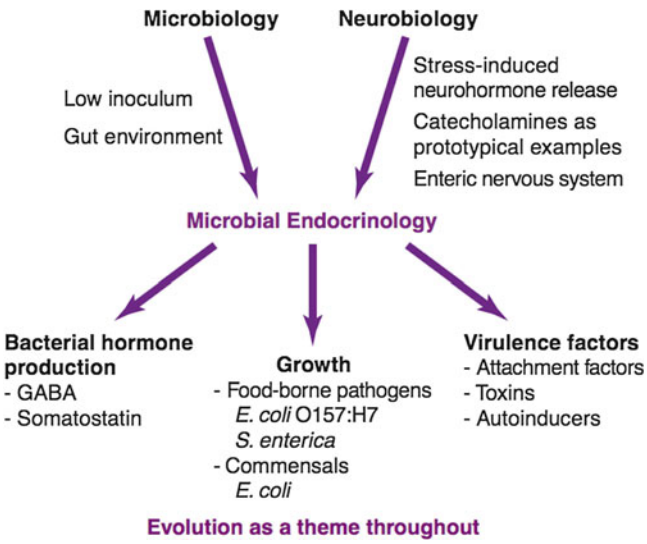

Fig. 5.2 Influence of microbiologic and neurologic factors on microbiota population structure and function (From Lyte M. Microbial endocrinology and infectious disease in the 21st century. Trends Microbiol. 2004;12(1):14–20, with permission)

Other bacterial signaling molecules that affect motility are just being discovered or have yet to be fully defined. Early studies revealed that infusion of bile acids, many of which are deconjugated by gut bacteria, into the human distal intestine stimulates local motility [82]. The G-protein-coupled bile acid receptor TGR5 is now thought to be an essential part of this bile acid motor reflex response [83]. An undefined product of the probiotic *E. coli* Nissle 1917 has myoelectric effects in human colonic strips [84], and membrane vesicles from *L. rhamnosus* JB-1 influence peristalsis in mouse colon via interactions with epithelial cells [85]. Further work is needed to define specific bacterial products and their site-specific mechanisms of action in the human intestine.

A fascinating link has emerged between commensal bacteria and intestinal motility via metabolism of serotonin, one of the key mediators of propulsive transit. Conventionally reared mice have threefold increased quantities of plasma serotonin compared to germfree animals [86, 87]. Germfree mice have reduced colonic expression of tryptophan hydroxylase 1 (*Tph1*), the rate-limiting gene in serotonin synthesis, and increased expression of the serotonin reuptake transporter [87]. Recent studies in germfree and gnotobiotic mice confirmed that gut microbes stimulate enterochromaffin cells to increase *Tph1* expression, raise intestinal and plasma serotonin levels, and increase GI transit rates [88, 89]. These studies also used culture models of enterochromaffin cells to implicate a number of microbial-derived molecules, including SCFAs, secondary bile acids, and intermediates of vitamin synthesis, as stimulating serotonin production [88, 89]. Some of these secreted signals may cross the blood brain barrier, given that germfree mice also have altered hippocampal levels of serotonin metabolites [90]. Butyrate, in particular, increases quantities of serotonin through an inducible zinc finger transcription factor that binds directly to *Tph1*; mice lacking this gene known as ZBP-89 had lower intestinal and plasma levels of serotonin and were more susceptible to infection [91]. Notably, the presence of gut bacteria does not affect a second source of serotonin, *Tph2* in enteric neurons. Studies of *Tph2*-deficient mice reveal this enzyme is the more important isoform in terms of myenteric plexus architecture and constitutive intestinal transit [92]. Whether therapeutic remodeling of the microbiome to influence serotonin metabolism may have roles in FGIDs remains uncertain.

Host Factors

Complicating matters further is the fact that the host's motility itself influences the microbiome. In animal models, disruption of regular motor patterns produces SBBO [17–19]. In addition, analysis of stool obtained from healthy volunteers with pharmacologically altered GI transit times found a significant positive correlation between transit rate and total bacterial mass [93]. However, while some bacteria flourish during rapid transit, others prefer a static luminal environment. For example, in mice with congenital colorectal aganglionosis modeling Hirschsprung disease, there were both increased proportions of Bacteroidetes and decreased Firmicutes [94].

In addition to altering microbiota composition, host motility also affects microbial function. The controlled environment of an in vitro continuous culture system was used to confirm that flow rate is a key determinant of both composition and function of human fecal microbial communities [95]. In one example, fecal microbes obtained from adult volunteers with pharmacologically increased transit rates correlated with increased substrate fermentation into SCFAs and decreased pH of the culture medium; the opposite was true for microbes harvested from adults with decreased transit rates [96].

Mechanisms governing the associations between intestinal microbial composition and function are even less clear in human disorders of dysmotility, particularly given the coexistence of other host factors intimately linked to GI pathology including physiologic stress. Mouse models reveal that catecholamine release drastically increases certain intestinal microbial populations [97] and may prime the host mucosa to be more permissive to the attachment of enteric pathogens [98]. These and other host-derived factors must be considered in the context of GI diseases associated with altered rates of transit, including but not limited to irritable bowel syndrome (IBS), inflammatory bowel disease, acute gastroenteritis, and delayed gastric emptying.

In addition to physiologic stress, two recent studies convincingly show that intestinal transit time is inextricably linked to both diet and gut bacteria. The first report analyzed germfree mice, conventionally raised mice, and gnotobiotic mice colonized with a simple humanized microbiota. Transit rates in all animals were accelerated either pharmacologically with polyethylene glycol or via the diet with a nonfermentable polysaccharide, cellulose. In contrast, administration of fructooligosaccharide, a fermentable polysaccharide, decreased SCFA production and slowed transit rates only in mice with microbes. Similarly, germfree mice receiving fructooligosaccharide exhibited more rapid transit similar to that following administration of polyethylene glycol. Likewise, decreasing transit rates with a polysaccharide deficient diet was successful only in mice with intestinal bacteria. These experiments indicate that diet influences motility through both microbiota-dependent and microbiota-independent pathways (Fig. 5.3) [99]. In the second study [100], six groups of germfree mice were humanized by fecal microbes from six different environments: a twin pair from the United States discordant for obesity, a lean US consumer of a protein- and fat-rich primal diet, a Venezuelan living in the rural Amazon, a Bangladeshi living in an urban slum, and a Malawian from a rural village. These groups of mice were in turn fed a succession of different diets with carbohydrate, protein, and fat contents representative of each of the 6 donor types. These experiments found diet-dependent correlations between specific bacterial groups and whole-intestinal transit time. Fecal metabolomic analyses revealed deconjugated bile acids, which are metabolized from conjugated bile acids by bacterial bile salt hydrolases, to be associated with faster transit. Metatranscriptomic analyses revealed that a component of the Bangladeshi diet, turmeric, influenced transit times in a manner that was dependent on the amount of bile salt hydrolase activity present in the host [100]. These experiments illustrate not only the complexity of host-microbiome-diet interactions but also the utility of employing top-down, systems-based approaches to complex mechanism discovery.

Mechanisms of Cross Talk Between Microbiota and the Central Nervous System

In comparison to those governing motility, the mechanisms by which gut microbiota communicate with the CNS to influence processes such as pain perception and behavior are less well defined. Much of the current mechanistic knowledge has been obtained using a diverse array of labor-intensive animal model techniques. Neuronal function may be assessed using in situ gene expression or ex vivo patch-clamp action potential recording devices; visceral sensitivity can be assessed by measuring abdominal wall contractions or heart rate during colorectal or gastric distention via intraluminal balloon; and anxiety phenotypes can be replicated by assessing freezing behaviors or other responses to water-avoidant stress, open-field novelty tests, marble burying, and maternal separation of pups. These and other techniques have uncovered novel mechanisms of brain-gut-microbiota interactions in three main categories: modified signaling pathways in enteric nerves and epithelial cells which affect the CNS, CNS structural or functional changes, and induction of systemic responses that may influence host neurobiology.

Gut bacteria may have direct effects on sensory neurons. Infection of mice with *Campylobacter jejuni* increased the expression of the neuronal activation marker c-Fos both in vagal sensory ganglia and in the nucleus of the solitary tract, a region of the brain where vagal sensory inputs converge

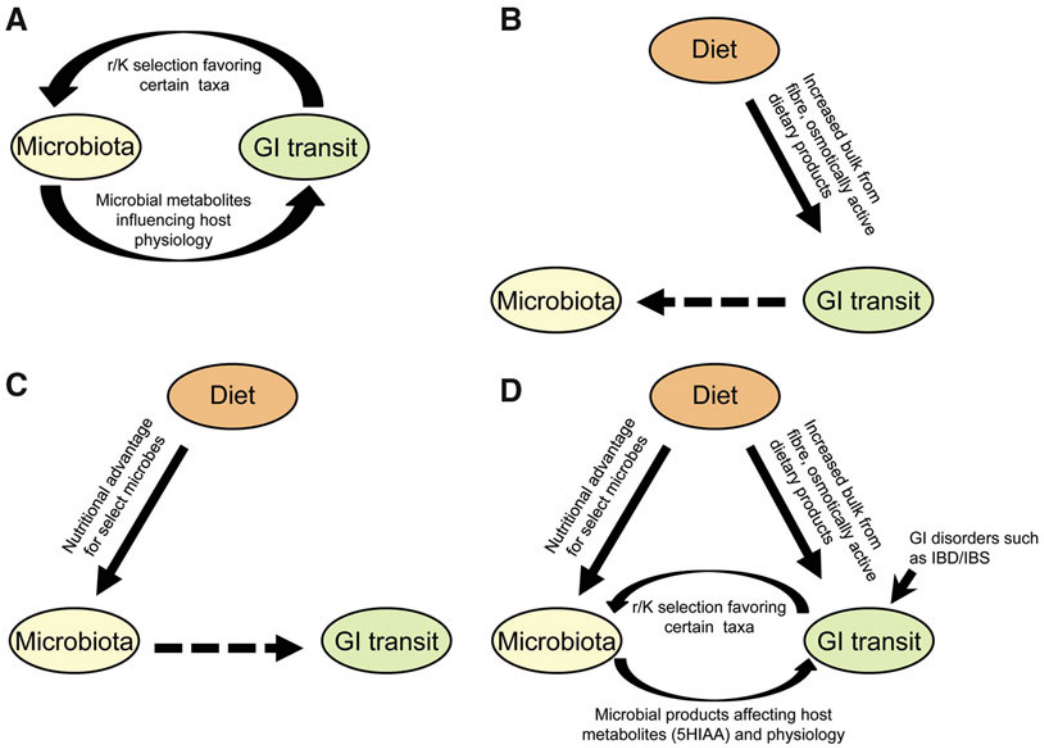

Fig. 5.3 Interactions between diet, intestinal microbiome, and GI transit rates (From Kashyap PC, Marcobal A, Ursell LK, Larauche M, Duboc H, Earle KA, Sonnenburg ED, Ferreyra JA, Higginbottom SK, Million M, Tache Y, Pasricha PJ, Knight R, Farrugia G, Sonnenburg JL. Complex interactions among diet, gastrointestinal transit, and gut microbiota in humanized mice. Gastroenterology. 2013;144(5):967–77, with permission)

[101]. Likewise, *Citrobacter rodentium* enhanced c-Fos expression in vagal sensory ganglia, while eliciting anxiety-like behavior patterns on open-field testing [102]. Sensory function also was altered in a postinfectious hypersensitivity model. Afferent neurons from mice infected with *Trichinella spiralis* demonstrated a biphasic response to ex vivo stimulation, showing hyposensitivity during the acute infection and then increased basal activity with hypersensitivity several weeks later. This finding appears to be partially mediated by altered serotonin metabolism and has potential relevance to postinfectious IBS [103]. Although most of the signals mediating communication of sensory information between pathogens and enteric nerves are unknown, one study revealed, as measured by increased excitability and expression of proinflammatory markers, that either lysates from *E. coli* cell walls or LPS activates mouse colonic nociceptive dorsal root ganglion neurons [104]. Further work remains to identify the specific bacterial secreted products that influence nociception and the ENS sensory pathways that these products activate.

Early studies with probiotics revealed that *Lactobacillus farciminis* minimizes the effect of partial-restraint stress on visceral hypersensitivity in mice, perhaps by inhibiting colonic mucosal expression of epithelial cell cytoskeletal contractile element phosphorylated myosin light chain [105]. Similarly, the probiotic *Lactobacillus reuteri* decreases dorsal root ganglion nerve firing and blunts the pain response to colorectal distention in rats [106]; this may occur by inhibiting a calcium-dependent potassium channel on neurons of the myenteric plexus thus affecting both sensory and motor reflex pathways [107, 108]. Another mechanism by which probiotics may reduce nociceptive neurotransmission was elegantly illustrated in a classic study by Rousseaux et al. [109] where *Lactobacillus acidophilus* induced upregulation of μ-opioid and cannabinoid receptor 2, mediators of nociceptive signal transmission. This occurred both in enterocyte cultures and in murine models, leading to increased rat colorectal distention pain thresholds [109]. Decreased enteric neuronal excitability also has been demonstrated in mice treated with the probiotic *Bifidobacterium longum* [110, 111].

It is important to note that neuron-modulating effects may not be restricted to specific pathogens and probiotics. Normal activity by intrinsic primary afferent neurons depends on the presence of intestinal microbes in general. Neurons harvested from germfree mice demonstrated lower resting membrane potentials, decreased excitability [112], and decreased responsiveness to agonist-induced firing [113].

Recent data indicate that CNS structure and function is influenced by the intestinal microbiota. Metabolomic analyses reveal that nearly 20 % of mouse cerebral metabolites are altered by the germfree state [114]. In a landmark study, Diaz Heijtz and colleagues [115] reported that germfree mice and gnotobiotic mice colonized by microbes as adults exhibit different behavior including both increased locomotor and decreased anxiety-like behavior. That gnotobiotic mice colonized in adulthood behaved like germfree mice suggests a critical early-life window of brain development mediated by a normal microbiota. The authors then used metabolite and gene expression analyses to correlate the altered behavior phenotype with processes influencing the development of neuronal circuits that mediate locomotor and anxiety behaviors [115]. Conventionally reared mice with antibiotic-depleted microbiota demonstrated similar behavioral changes, correlating with increased hippocampal expression of brain-derived neurotrophic factor, a key mediator of memory, learning, anxiety, and depression [116]. A different study linked behavior changes in germfree mice to altered CNS expression of not only brain-derived neurotrophic factor but also N-methyl-D-aspartate receptor subunit NR2B and serotonin receptor 1A [117]. Other mediators of CNS effects have yet to be identified. For example, *Acinetobacter lwoffii,* an organism that blooms during antibiotic treatment of rats with chemically induced fulminant hepatic failure, produces an uncharacterized, inactive plasma compound that appears to be converted in the brain to a benzodiazepine receptor ligand that worsens hepatic encephalopathy [118]. Behavioral and gene expression or metabolite changes in the brain also have been reported in conventionally reared mice infected with *Trichuris muris* [119] or *C. rodentium* [120] or in animals receiving either the probiotic *L. rhamnosus* [121] or *Bifidobacterium infantis* [122, 123] by unknown mechanisms. Whether these reported CNS effects in conventional mice are attributed to direct effects of these individual bacteria or to their secondary alterations to the resident microbiome is unclear.

Recent data from studies in humans support some of the observations made in these mouse models. Administration of *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 reduced psychological distress and anxiety in healthy women in a double-blind trial [124]. In another double-blind trial in healthy women, consumption of a fermented drink containing *Bifidobacterium, Streptococcus,* and two strains of *Lactobacillus* altered brain activity as measured by functional magnetic resonance imaging (fMRI) [125]. Changes in fMRI were also seen in patients with cirrhosis and encephalopathy treated with the antibiotic rifaximin [126].

Gut microbes have been shown to alter systemic stress response and inflammatory pathways. Germfree mice have exaggerated ACTH and corticosterone responses to partial-restraint stress. This effect is both blunted by monocolonization with the probiotic *B. infantis* and exacerbated by monocolonization with enteropathogenic *E. coli*. Similar to the developmental window revealed for the influence of gut microbes on locomotor and anxiety-like behavior, the exaggerated stress response was ameliorated by early but not late colonization of germfree animals [127]. Bacteria can alter the body's response to stress through inflammatory pathways. Sun et al. found that exposing mice to 10 days of water-avoidant stress caused several inflammatory-related changes including increased corticotropin-releasing hormone, inhibition of the NLRP6 inflammasome, intestinal inflammation, and microbial dysbiosis. The dysbiosis was characterized by decreased Bacteroidetes, increased Firmicutes, and increased γ-Proteobacteria. Intriguingly, healthy mice acquired dysbiosis, increased levels of corticotropin-releasing hormone, and decreased NLRP6 when co-housed with mice naïve to stress. Each of these effects was ameliorated by giving the co-housed mice either broad-spectrum antibiotics or a mixture of 3 lactic acid-producing probiotics [128]. These data suggest that a portion of the physiologic effects of psychological stress may be driven by various microbial populations.

In summary, gut bacteria exert a myriad of effects on genes, metabolites, and physiologic processes governing multiple neurogastroenterological phenomena. As we continue to develop technology pipelines that enrich our understanding of both known and novel intestinal microbes along with their myriad of secreted products, we will continue to discover new mechanisms of communication between the microbiota and mammalian CNS and new preclinical and clinical tools for maintaining the microbiome in a state of relative health [129] (Fig. 5.4).

Irritable Bowel Syndrome and Related Functional Disorders

Altered gut microbiota populations have been found in patients with FGIDs. Balsari and colleagues were the first to show, using culture-dependent techniques, that fecal microbial populations from adults with IBS were different than those from healthy adults. Compared to controls, they found that symptomatic patients had decreased coliforms, lactobacilli, and bifidobacteria [130]. Altered microbial populations in IBS were subsequently reported using more advanced techniques including real-time PCR [131], PCR combined with a phylogenetic microarray [132], PCR with HPLC-based bile acid profiling [133], percent G+C profiling with a 16S rRNA clone library [134], fluorescent in situ hybridization on rectal biopsy samples [135], and ultimately high-throughput 16S rRNA gene sequencing [136, 137].

Only recently have microbial communities in pediatric IBS been defined. Children with IBS diagnosed by Rome III

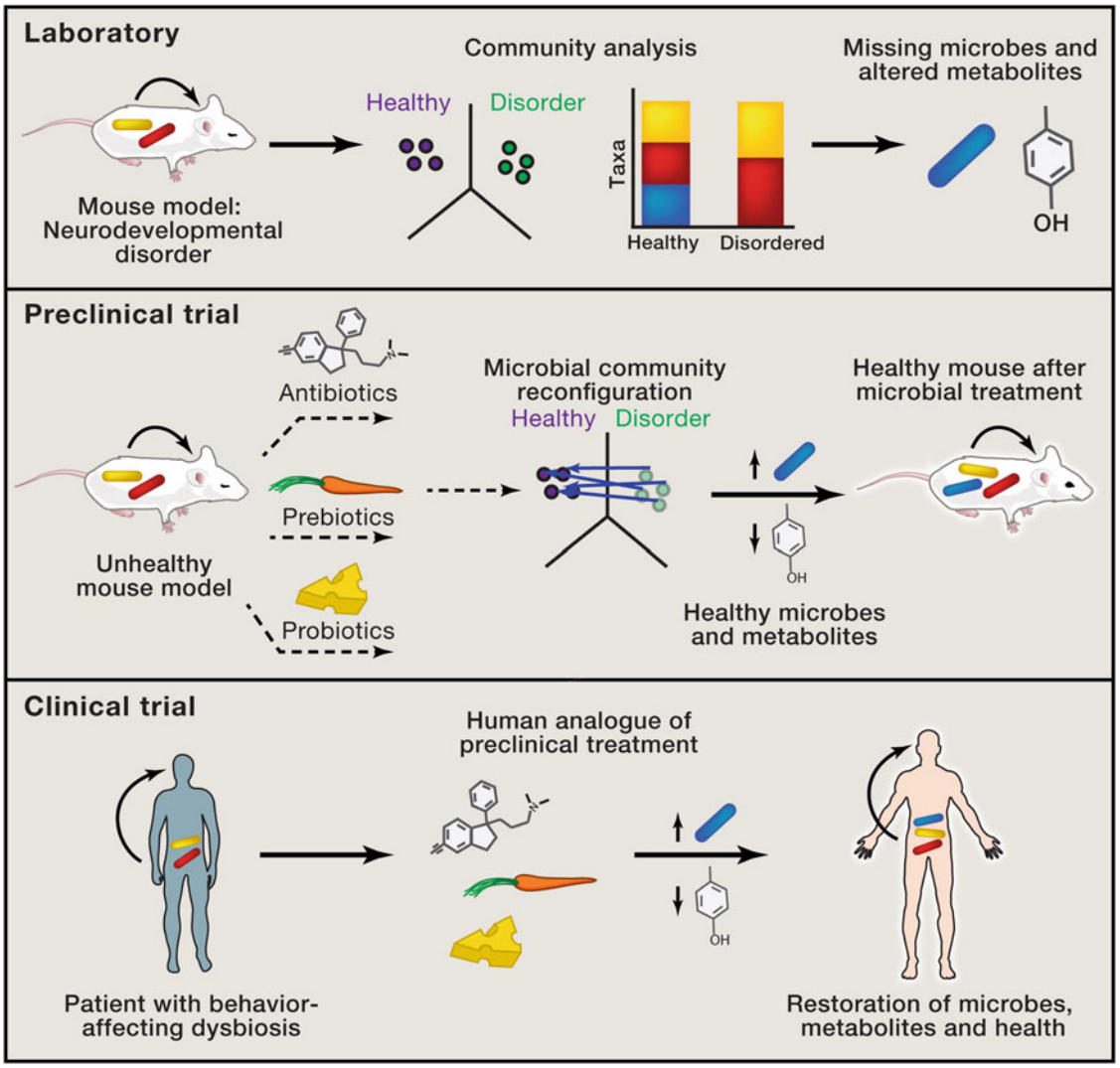

Fig. 5.4 Potential pipeline for development of therapeutics for disorders of neurogastroenterology (From Gilbert JA, Krajmalnik-Brown R, Porazinska DL, Weiss SJ, Knight R. Toward effective probiotics for autism and other neurodevelopmental disorders. Cell. 2013;155(7):1446–8, with permission)

criteria had higher proportions of γ-Proteobacteria, a class containing multiple pathogens such as *Haemophilus parainfluenzae*. In addition, supervised machine-learning algorithms identified specific taxonomic units that distinguished with 98.5 % accuracy children with constipation-predominant from those with unsubtyped IBS [138]. In another study, children with diarrhea-predominant IBS had increased proportions of the genera *Veillonella, Prevotella, Lactobacillus*, and *Parasporobacterium* and decreased proportions of *Bifidobacterium* and *Verrucomicrobium* [139]. Given these associated changes in gut microbiota composition, manipulation of the microbiome has the potential to address processes that may contribute to IBS pathogenesis including microbial fermentation, nociceptive pathways, inflammatory signaling pathways, and abnormal intestinal motility. Multiple meta-analyses (Table 5.1) have evaluated the more than 60 published clinical trials that examine effects of probiotics in patients with IBS. One early review of eight randomized, placebo-controlled trials found that probiotics conferred a small but statistically significant improvement in symptoms vs. placebo [140]. Other meta-analyses evaluating the efficacy of probiotics for adults with IBS found similarly small yet statistically significant effects [141–145]. The largest pooled relative risk for symptom improvement (RR 17.6, 95 % CI 5.1–61) was reported for adults receiving *Lactobacillus* spp. for IBS, although beneficial effects reported with *Lactobacillus* for children in this analysis were less striking [146].

To date, two meta-analyses have evaluated probiotics for functional abdominal disorders exclusively in children. In a review of nine trials enrolling 741 children, different probiotic strains significantly improved functional abdominal pain

Table 5.1 Select systematic reviews of randomized controlled clinical trials that tested microbiota manipulations in the treatment of neurogastroenterological disorders

Indication	Patient population	N	Species/intervention	Result	Ref
Irritable bowel syndrome	Children and adults with IBS established by Rome criteria	1011	*Bifidobacterium* spp. *Lactobacillus* spp. *P. freudenreichii* VSL#3	Improved clinical outcomes [RR 1.2, 95 % CI, 1.07–1.4]	Nikfar et al. [140]
	Children and adults with IBS	1404	*B. subtilis* *Bifidobacterium* spp. *E. coli* *Lactobacillus* spp. *L. lactis* *P. freudenreichii* *S. boulardii* *Streptococcus* spp. VSL#3	Reduced global IBS symptoms [RR 0.77, 95 % CI 0.62–0.94] Reduced abdominal pain [RR 0.78, 95 % CI 0.69–0.88]	McFarland and Dublin [141]
	Adults >16 years with IBS	1650	*B. subtilis* *Bifidobacterium* spp. *Lactobacillus* spp. *L. lactis* *P. freudenreichii* *Streptococcus* spp. VSL#3	Lowered risk of persisting symptoms [RR 0.71, 95 % CI 0.57–0.88] Improved IBS score [SMD −0.34, 95 % CI −0.60 to −0.07]	Moayyedi et al. [142]
	Children and adults with IBS	>1225	*Bifidobacterium* spp. *Lactobacillus* spp. *P. freudenreichii* *Streptococcus* spp. VSL#3	Improved overall symptoms [RR 1.6, 95 % CI 12–22] Improved overall symptoms [SMD 0.23, 95 % CI 0.07–0.38]	Hoveyda et al. [143]
	Children and adults with IBS	440	*Lactobacillus* spp.	Improved overall symptoms [RR 7.7, 95 % CI 2.3–25]	Tiequn et al. [146]
	Children and adults with IBS	1793	*Bifidobacterium* spp. *E. faecalis* *E. coli* *Lactobacillus* spp. *L. lactis* *P. freudenreichii* *S. thermophilus*	Improved global IBS symptoms [RR 2.5, 95 % CI 1.1–5.2] Improved abdominal pain score [RR 2.0, 95 % CI 1.1–3.4]	Didari et al. [145]
	Adults with IBS and IBS-type symptoms	234	Metronidazole Neomycin Rifaximin	Improved IBS symptoms [RR 2.0, 95 % CI 1.2–3.4]	Rezaie et al. [154]
IBS and CIC	Adults >16 years	2575	*B. subtilis* *Bifidobacterium* spp. *E. faecalis* *E. coli* *Lactobacillus* spp. *L. lactis* *P. freudenreichii* *S. boulardii* *Streptococcus* spp. VSL#3	Lowered risk of persisting IBS symptoms [RR 0.79, 95 % CI 0.70–0.89] Increased mean stools/week in CIC by 1.49 [95 % CI 1.02–1.96]	Ford et al. [144]
Functional Gastrointestinal Disorders	Children and adolescents with FGIDs established by Rome III criteria	741	*Bifidobacterium* spp. *Lactobacillus* spp. VSL#3	Improved outcomes in abdominal pain-related FGIDs [RR 1.50, 95 % CI 1.22–1.84] No significant improvement for defecation-related FGIDs	Korterink et al. [147]
Abdominal pain-related FGIDs	Children up to 18 years with FGIDs established by Rome II criteria	290	*L. rhamnosus*	Higher rate of treatment responders [RR 1.31, 95 % CI 1.08–1.59]	Horvath et al. [148]

CI confidence interval, *CIC* chronic idiopathic constipation, *FGIDs* functional gastrointestinal disorders, *IBS* irritable bowel syndrome, *SMD* significant mean difference, *VSL#3* probiotic mixture containing 3 bifidobacteria (*B. breve, B. infantis, B. longum*), 4 lactobacilli (*L. acidophilus, L. bulgaricus, L. paracasei, L. plantarum*), and *Streptococcus thermophilus*

symptoms, although no significant improvement of defecation-related symptoms was reported [147]. Another meta-analysis reviewed three placebo-controlled trials of *L. rhamnosus* GG enrolling 290 children with abdominal pain-related FGIDs by Rome II criteria. This analysis reported a modest but significant benefit for *L. rhamnosus* GG, due primarily to a benefit for children with IBS [148]. These meta-analyses are complicated by multiple factors, including heterogeneity of the FGIDs and the use of different microbial species, strains, combinations of agents, doses, and durations of therapy. Combining data from such a heterogeneous group of studies limits the information gleaned from specific interventions. As such, any conclusions based on a small number of studies of varying quality must be interpreted with caution.

Although antibiotic use for nongastroenterological indications may increase the risk of developing functional bowel symptoms [149, 150], there is also evidence that manipulating the microbiota through antibiotic therapy may be beneficial in IBS. Pimentel and colleagues studied a subset (78 %) of adults with IBS meeting Rome I criteria who had a positive lactulose hydrogen breath test suggestive of SBBO. These subjects were treated with a 10-day course of oral antibiotics after which they returned for repeat breath testing and symptom assessment. Patients with a negative breath test at follow-up reported significant improvements in diarrhea and abdominal pain; furthermore, half of the follow-up breath test-negative patients no longer met criteria for IBS [151]. Subsequent double-blind placebo-controlled trials enrolling adults with Rome criteria FGIDs found significant but modest benefits with the nonabsorbable antibiotic rifaximin [152, 153]. The only meta-analysis that has evaluated the effectiveness of antibiotics for IBS found a small but statistically significant benefit. However, the authors warned there is overall insufficient evidence to recommend the routine use of antibiotics in this setting [154]. In children with IBS, a double-blind placebo-controlled trial did not find rifaximin to be superior to placebo [155].

Dietary interventions targeting the intestinal microbiota show promise in treating FGIDs. Ingestion of a fermentable prebiotic may stimulate the growth or activity of a beneficial group of commensal bacteria [5]. The most commonly studied prebiotics are fructooligosaccharides, a fermentation substrate for multiple genera including *Bifidobacterium* in the production of SCFAs. Fructooligosaccharides demonstrated beneficial effects in randomized placebo-controlled trials of adults with IBS [156] and minor FGIDs [157]. Likewise, a prebiotic mixture containing galactooligosaccharides increased fecal bifidobacteria counts and improved symptoms in adults with Rome II IBS [158]. However, the paucity of published studies precludes evidence-based recommendations regarding prebiotics for FGIDs [144]. Fiber supplementation, which alters colonic microbiome composition and function [159], has been used as a therapy in adults and children with IBS. A meta-analysis [160] which included two fiber supplementation studies in children with functional abdominal pain [161, 162] did not demonstrate significant efficacy. However, the quality of these studies limits their interpretation. Recently, psyllium fiber supplementation was found to decrease abdominal pain frequency in children with IBS [163]. A meta-analysis of fiber supplementation in adults with constipation-predominant IBS (including 3 studies) found efficacy [164]. A clear correlation of dietary fiber supplementation with changes in gut microbiome composition correlating with IBS symptom improvement has not been established [163].

As an alternative strategy, fermentable carbohydrates, which are associated with increased intraluminal gas production and osmotic activity [165, 166], may be restricted in the diet. An open-label low carbohydrate diet improved symptoms in adults with diarrhea-predominant IBS [167]. Several studies have evaluated the role of a low *f*ermentable *o*ligosaccharide, *d*isaccharide, *m*onosaccharide, *a*nd *p*olyol (FODMAP) diet in reducing symptoms in adults and children with IBS. One randomized, double-blind, quadruple-arm, placebo-controlled rechallenge trial found significantly higher symptom severity scores in adults with IBS given fructose, fructans, or a combination of the two versus glucose (placebo) [168]. Another randomized, double-blind, crossover trial found amelioration of GI symptoms (including abdominal pain and bloating) in adults with IBS while on the low FODMAP diet [169]. In children with Rome III IBS, both an open-label pilot study and a randomized, double-blind, crossover study found that a low FODMAP diet ameliorated abdominal pain frequency [170, 171]. In addition to ameliorating GI symptoms in those with IBS, low fermentable substrate diets have been found to alter gut microbiome composition and function (decreased fermentation). A low carbohydrate diet decreased gas (hydrogen and methane) production in adults with IBS [165]. Halmos et al. found that when compared to a typical Australian diet, a low FODMAP diet was associated with higher fecal pH, greater microbial diversity, and reduced total bacterial abundance [172]. The authors also found decreased hydrogen production while on the low FODMAP diet [172]. Staudacher et al. found that in comparison to a habitual diet, a 4-week low FODMAP diet lowered both concentrations and proportions of bifidobacteria [173]. In children with IBS, Chumpitazi et al. also found decreased hydrogen production while on the low FODMAP diet [171].

Given that commensal microbes utilize a wide variety of organic substrates for fermentation, a deeper understanding of how the metabolic machinery encoded within the intestinal microbiome affects functional abdominal symptoms

may facilitate the discovery of novel prebiotics that have predictable effects on intestinal physiology. In this respect, baseline gut microbiome composition may play a role in determining whether IBS symptoms are ameliorated during a low FODMAP diet. In children with Rome III IBS, those who markedly improved on a low FODMAP diet had a different gut microbiome composition at baseline (prior to any dietary intervention) in comparison to those who did not. These responders were enriched in taxa with known greater saccharolytic metabolic capacity (e.g., *Bacteroides*, Ruminococcaceae, and *Faecalibacter prausnitzii*) [171]. Further studies are needed to determine whether one's gut microbiome may predict dietary intervention efficacy.

Prospectus

At present we have only begun to understand the numerous and complex ways in which intestinal microbes impact human neurogastroenterology. As next-generation sequencing and related technologies, including statistical methods for drawing meaning from these enormous and complex data sets, continue to evolve at a rapid pace, these new tools will further add to our knowledge base. For example, whole metagenome sequencing ushered in a paradigm shift, as we begin to understand intestinal microbial communities in terms of their function rather than simply their composition. Improved approaches to sequencing the intestinal pool of microbial mRNA, or metatranscriptomics, will also shed light on microbiome function. Another important avenue of research will be to explore the contributions of nonbacterial members of the microbiota, including the virome (both eukaryotic viruses and phages) and the mycobiome. As metabolomics approaches become more readily available, the measurement of microbial metabolites in multiple body compartments will lend further insight into beneficial or harmful functions conferred by specific microbes and microbial populations. Another key challenge is to understand the structure and function of the mucosal microbiota; these microbial communities are much more difficult to access and study from patients and, particularly, healthy controls, compared to luminal microbes found in feces.

Understanding how microbes influence neurogastroenterological processes will be essential to determining whether altered microbial communities result from disease states (e.g., dysmotility or inflammation) or whether altered populations actually contribute to pathology of FGIDs. The ultimate goal is to facilitate more rational selection of probiotic strains, combinations of strains, and prebiotics for therapeutic trials based on mechanistic principles. Given the multitude of effects conferred by gut microbes on host neurobiology, it is possible that in the future gastroenterologists will be able to identify unhealthy components of the gut microbiome of patients with IBS and other FGIDs and through strategic manipulations may replace pathologic microbial functions with those that promote health.

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Integration of Biomedical and Psychosocial Issues in Pediatric Functional Gastrointestinal and Motility Disorders

6

Miranda A.L. van Tilburg

Treating gastrointestinal symptoms in children is often more difficult than it may seem. Consider the following case:

Johnny is a 6-year-old child who presents with nausea and abdominal pain. Upon history taking, the child appears to experience early satiety and some minor weight loss. You notice pallor and irritability. After thorough diagnostic work-up, John is diagnosed with delayed gastric emptying. The family is sent home with a prescription for erythromycin and referral to a dietician. Several months later, Johnny returns to you and appears to be doing well. Pallor has disappeared and weight loss has been stopped. Nevertheless, problems continue at home around feeding. Johnny still refuses food and continues to complain of nausea and abdominal pain. You suspect psychological factors may be playing a role. The symptoms started around the time Johnny's parents got a divorce. Mother seems anxious and Johnny is out of school regularly around fear of symptoms.

This scenario is recognizable for many clinicians working with children who suffer from functional gastrointestinal and motility disorders. Psychosocial factors often play a role in these disorders, and no clinician working with this group of patients will deny their influence. But the interpretation of how psychological symptoms affect the onset and maintenance of these disorders varies considerably among clinicians. Are psychological issues primary causes of some disorders? Can psychological disturbances affect digestive processes? In the case of Johnny: Were the continuation of his symptoms after successful treatment of the gastric emptying primarily due to (1) anxiety of his family, who may too easily over-interpret normal symptoms as signaling disease, or (2) was there a behavioral component to his symptoms in the first place that was not addressed with medication therapy, thereby leading to less effective treatment? Answers to some of these questions can affect the course of suggested treatments for Johnny and other children like him. In this chapter, first, the theoretical models explaining the role of psychosocial issues in health and disease will be discussed. These are implicit working models guiding clinical care and scientific research and are important to explore. Then, the current scientific evidence for the role of psychosocial factors on physiological functioning will be presented.

Psychological Issues in Health and Disease

Biomedical Model: A Symptom Has Either a Physiological or Psychological Origin

Under guidance of the biomedical model, medicine has seen one of the greatest advances over the past centuries. This model has been responsible for some of the most impressive discoveries of modern medicine such as the development of penicillin, vaccines, etc. It is still widely popular today among many clinicians and patients. The biomedical model envisions a direct relation between disease and symptom: Cause A will lead to symptoms B. The more disease causing A is present, the more symptoms will be observed. If A is eradicated, the symptoms will disappear. This straightforward model of health and disease focuses primarily on biological origins but argues that in lieu of a disease or structural abnormality, psychological factors can cause symptoms. For example, if no biomedical reason can be found for stomachaches (such as lactose intolerance), then these symptoms can be attributed to psychosocial distress, i.e., anxiety or school avoidance. The biomedical model is simple and elegant but completely ignores contextual influences on health and disease: Symptoms are either caused by biological or psychological causes. This straightforward and appealing approach has led to the notion that if symptoms are not in "the body," it must be "all in the head." It also explains our fascination with drugs as a "quick fix" for *real* symptoms worthy of a clinician's time while behavioral or supportive therapy have

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become synonym to treating symptoms that are either feigned or a result from being "crazy" and not belonging in a physician's office.

Biopsychosocial Model: Symptoms Can Be Altered by Psychosocial Processes

By the mid-1970s the well-established biomedical model started to show little cracks. It became clear that there was no perfect association between biomedical processes and symptoms. For example, under the biomedical model, the frequency and amount of gastric acid refluxing into the esophagus should explain the intensity of heartburn complaints. However, there are patients with very severe acid reflux for years, who are minimally symptomatic until developing Barrett's esophagus. On the other hand, there are others with minimal acid reflux whose life is severely affected by their symptoms. The only way to explain these findings with the biomedical model is to see the first person as a "tough" or stoic, silently suffering while continuing with his/her life, while the second is a "wimp" complaining at the tiniest bit of discomfort. The first elicits admiration and the second contempt. However, imperfect associations between biomedical processes and symptoms are so ubiquitous that they seem to be the rule rather than the exemption. The biopsychosocial model, first proposed by Dr. Engel [1], posits that biochemical alterations do not directly translate into illness. The appearance of symptoms is an interplay between many factors including biomedical, psychological, and social factors, e.g., bacteria A leads to more symptoms under stressful circumstances.

The biopsychosocial model has been widely adopted by researchers and clinicians to explain health and disease and is particularly useful for understanding and studying functional gastrointestinal disorders. There is a robust literature describing the influence of both physiological and psychological factors on the illness presentation of functional gastrointestinal disorders, in particular irritable bowel syndrome (IBS). These studies will be discussed later in this chapter.

System Theory: Physiological and Psychological Processes Are Constantly Interacting to Cause Symptoms

Although the biopsychosocial model was presented by Dr. Engel as a system theory, it is nowadays often presented in a reductionist way. Some authors reduce mental and social phenomena to basic biological phenomena, such as activation of the autonomous or central nervous system (CNS) and hypothalamic-pituitary-adrenal (HPA) axis [2]. Johnny from our case at the beginning of the chapter may be anxious which leads to CNS and HPA axis activation, interacting through the brain-gut axis with the enteric nervous system culminating in gastrointestinal symptoms. Systems theory acknowledges that psychosocial processes undoubtedly have biological correlates. However, it argues that the different systems—biological, psychological, and social—interact with each other but cannot be reduced to the lowest, molecular, level. The reasoning behind this is simple: we cannot understand the meaning of psychosocial processes by purely studying its biological correlates; subjective phenomena are equally important.

The biopsychosocial model is also sometimes reduced to a hierarchy of unidirectional cause and effects relationships which includes causes, precipitants, modulators, or sustaining forces [3]. In Johnny's case, anxiety and delayed gastric emptying can be thought to independently cause or sustain his symptoms, and it is up to the physician to decide which one is most important and thus should be treated first. Viewing psychosocial and biomedical factors as somewhat independent processes largely denies the reality of the situation in which there are feedback loops between all parts of the system. Johnny's delayed gastric emptying caused pain and fullness, which made him anxious around food. His fears of having pain after a meal in turn may have led to hypervigilance and increased the sensitivity of his nerves to normal digestive processes thereby worsening his symptoms. Thus, anxiety is both cause and effect in this circular loop.

Systems theory is an attempt to understand these complex feedback loops over time and discovering the interrelated causes that sustain specific symptom over time. Unfortunately, such integrated models of proximal causes and effects over time are difficult to study. The need for complex study designs and statistical methods has seriously hampered the testing of systems theory in functional gastrointestinal and motility disorders. Recent developments of system theory methodology in other fields show promise for application in functional gastrointestinal and motility disorders.

The Brain-Gut Axis

Nowadays, the role of psychosocial variables in functional gastrointestinal and motility disorders is widely recognized, and the biopsychosocial approach is commonly endorsed in explaining these disorders. The biopsychosocial model postulates that psychosocial factors can interact with the gut through the brain-gut axis: the bidirectional communication between the enteric nervous system in the gut and the brain. This means that emotions and thoughts have the capability to affect gastrointestinal sensation, motility, and inflammation. Reciprocally, gastrointestinal processes are able to affect perception, mood, and behavior. Dysregulation of the brain-gut axis is thought to be at the core of many functional gastrointestinal disorders.

With regularity the question is asked whether psychological issues are a cause or consequence of the brain-gut axis dysregulation. Some authors have found increased anxiety before a diagnosis of functional gastrointestinal and motility disorders [4], while others have argued that increased psychosocial distress may be a consequence of having to deal with a chronic, unpredictable condition [5]. A large community-based study found that both positions may be right: psychosocial comorbidity was as likely to be present *before* as *after* seeking care for abdominal pain [6]. The question is if it really helps to know which one came first. If we conceive of our body as a system in which psychosocial and biomedical factors interact continually, then the question of what came first is not relevant. Both factors will interact to cause symptoms and understanding the disorder is exploring this interaction. For example, in the case of fecal incontinence, we don't ask if the child was constipated first and then became anxious about evacuation of large bowel movements or anxious about potty training and then experienced large stools due to withholding. Both may be true and will lead to the same symptom: fecal incontinence. Both factors need to be addressed to ensure successful resolution of symptoms. Thus, rather than trying to solve the "chicken-and-egg" dilemma, we should focus on understanding how the different components of the system interact to create these symptoms. In the following section, we will summarize the literature on psychosocial influences on functional gastrointestinal and motility disorders.

Psychosocial Influences on Functional Gastrointestinal and Motility Disorders

There are many psychosocial aspects relevant to functional gastrointestinal and motility disorders such as personality [7], self-esteem [8, 9], and early childhood experiences [10, 11], to name only a few. Out of all the possibly relevant psychosocial factors, the most often studied is the concept of stress. We all know what stress is and what it feels like. However, defining stress is more elusive than it seems. First, there are the events that may be stressful: being stopped by a policeman for speeding, giving a speech in front of several colleagues, and taking your child to the emergency room. These are called stressors. Second, there are individual reactions to stress: feelings of anger/fear, trouble in concentrating, and physical reactions such as accelerated heartbeat, tensed muscles, and increased perspiration. It is important to realize that not all potential stressors lead to stress reactions and that stress can be both positive and negative. What is stressful for one person may be pleasurable to another or have little impact whatsoever to a third person. A parachute jump or deep sea dive may elicit enormous fear and anxiety in some, while others find it highly pleasurable, and for very experienced professionals, it may be just a simple routine. Therefore, stress is a subjective experience created by the appraisal of an environmental demand as harmful, threatening, or challenging and appraisal of our ability to meet this demand [12]. If a person has adequate resources to deal with a difficult situation, he or she may not experience stress; but if the demand (almost) exceeds one's resources, a person will be under a great deal of stress. When the term "stress" is used, it may refer to (1) the stressors, which are usually major life events such as trauma, abuse, or divorce, but can also be the cumulative effect of small daily hassles; (2) the subjective experience of stress which is usually measured by self-reports of perceived stress; and (3) stress reactions which includes behavioral (e.g., withdrawal or confrontation), emotional (e.g., anger, fear, anxiety, depression), and physiological reactions (e.g., skin conductivity, blood pressure, cortisol, and catecholamines). Thus, stress in addition to being itself is also causing itself and resulting itself. It is important to realize which aspect of stress is being referred to when reading and interpreting the scientific literature on stress.

Stress can be felt in the gut. We are all familiar with the typical butterflies associated with young love, feeling squeamish when being forced to deliver bad news, and the run to the bathroom before the start of an important race or game. Stress has been found to alter gut functioning. It has effects on GI sensory, motor, and immune functioning, which are also etiological pathways for many functional gastrointestinal and motility disorders.

Stress and Gastrointestinal Motor Functioning

Motility disturbances are a hallmark symptom of many functional gastrointestinal and motility disorders which may result in symptoms such as altered stool consistency, nausea, or bloating. There is evidence to suggest that stress induces changes in motility. For example, under stressful conditions, gastric emptying decreases and colonic transit accelerates [13]. These stress-induced motility changes are caused by increases in corticotrophin-releasing factor (CRF), especially CRF_1. CRF is best known as the principal instigator of the physiological response to stress through the hypothalamic-pituitary-adrenal (HPA) axis, and CRF 1 receptors have been found to regulate behavioral reactions to stress [14–17]. Brain CRF stimulation is associated with accelerated colonic transit, defecation, and diarrhea and stimulates similar brain areas as anxiety and depression [18]. But the effects of stress on motility seem to also operate outside of this system. It has been reported that activation of CRF receptors in the brain induces propulsive motor function and diarrhea without involving the HPA axis, but rather through stimulation of autonomic nervous system [19, 20] such as the stimulation of the sacral parasympathetic outflow [21]. Central CRF

stimulates the vagal nerves innervating the proximal colon which results in release of colonic serotonin [19, 22]. Serotonin is involved in various gastrointestinal motility processes such as the gastric accommodation reflex, the small bowel transit, and the colonic response to feeding [23, 24]. Therefore, serotonin abnormalities in the gut can lead to motility disturbances in functional gastrointestinal and motility disorders [23, 24]. This is supported by the fact that medications aimed at altering gut serotonin have been found to be effective in treating several functional gastrointestinal and motility disorders including IBS, constipation, functional dyspepsia, and gastroparesis [23, 24]. In addition to motility, CRF receptors have also been implicated in visceral hypersensitivity and immune functioning (for an overview see Tache et al. [18]).

Stress and Gastrointestinal Sensory Functioning

One of the most consistent findings in painful functional gastrointestinal and motility disorders is visceral hypersensitivity. Hypersensitivity to gut distension—the reporting of first sensation of pain at lower levels of pressure than normal—has been found in more than half of adult patients who suffer from IBS and functional dyspepsia [25]. Visceral sensitivity is usually measured by using the barostat technique. The barostat inflates a balloon to different pressure levels in the stomach, colon, or rectum while the patient is asked to report level of discomfort and pain (for guidelines on using the barostat in children, see van den Berg et al. [26]). As the barostat technique is invasive, studies in children are limited, but similar findings as in adults have been reported showing that visceral hypersensitivity is a common phenomenon in children with painful functional gastrointestinal disorders [26–30]. In addition, visceral *hypo*sensitivity in the rectum has been reported in children with constipation [31, 32]. Reduced sensation in the rectum corroborates the fact that these children do not easily feel an urge to defecate.

The role of stress on visceral sensitivity has only been examined in abdominal pain-related functional gastrointestinal disorders. Many studies have found lower pain thresholds in reaction to stress—which is equivalent to more easily reporting pain under stress. Studies in rats have shown that early-life stress is associated with colonic hypersensitivity in adulthood [33–39]. In fact, early-life stress induced visceral hypersensitivity which was transferrable to the next generation in mice, possibly due to changes in maternal care [40]. Less conclusive evidence is available for acute stress and chronic stress in adulthood, with effects dependent on various factors such as previous experiences, diurnal variation in stress reactivity, etc. [39], One study reported that stress in adult mice leads to increased visceral hypersensitivity only if combined with an infection [41], which mimics the findings of post-infectious IBS in humans. In humans, acute stress, induced by cold-water hand immersion (physical stressor) or dichotomous listening (mental stressor), seems to reduce pain thresholds as well [42, 43]. But other types of stressor have yielded mixed effects. Past stressful experiences (e.g., abuse history) and psychological distress (e.g., anxiety or depression) have been associated with decreased pain thresholds in some studies [27, 44–47], increased in others [48], while others have reported no effects of stress at all [27, 46, 49–51]. Thus, most studies report increased sensitivity with stress, but some did not find any effects, and one study actually found decreased sensitivity [52]. The reason for the inconclusive evidence may be related to the way visceral sensitivity is measured. In most barostat protocols, increasing levels of pressure are presented to the patient who is asked to indicate first perception of discomfort. This experimental design is believed to be vulnerable to psychological response biases in particular fear of pain [53]. Naliboff and colleagues found that when offering unpredictable changes in volume, differences in pain thresholds between IBS patients and controls disappeared [54]. Dorn and colleagues added to these findings by showing that rather than increased neurosensory sensitivity (the ability to discriminate between pressure levels), lower pain thresholds in IBS are explained primarily by an increased psychological tendency to report pain [55]. One of the nonsensory cues that influence pain threshold ratings is hypervigilance to symptoms. IBS patients have a higher tendency to label visceral sensations as unpleasant during barostat testing [54]. Thus, visceral hypersensitivity can either be caused by hypervigilance or perceptual sensitivity, and both may have associations with stress. Dorn found some indication that increased psychological distress is associated with hypervigilance, but others have not been able to replicate this observation [54–56].

If we assume that under certain circumstances, stress can affect visceral sensitivity, an important question becomes at what level in the neural system these effects are most dominant. Sensations from the gastrointestinal tract are relayed to spinal dorsal horn. Visceral sensory information is then conveyed to supraspinal sites and finally to cortical areas where they are perceived [57, 58]. Descending emotional pathways via the periaqueductal gray to the dorsal horn can amplify or suppress new afferent signals from the gut. Amplification of these signals can occur at any level in this neural pathway. Evidence is building that the central nervous system is an important site of modulating the pain response. Brain responses to visceral stimuli are increased in IBS patients compared to controls in areas related to conscious experience of visceral sensations (specifically the insular cortex) as well as areas related to emotion modulation and emotional response to threat including the anterior cingulate the cortex, the hypothalamus, and the amygdala. In addition, structural

changes in the brain have been described in IBS, such as decreased gray matter density in areas associated with corticolimbic inhibition and increased gray matter density in areas involved in stress. Thus, IBS patients tend to respond with more affective and attentional responses to visceral stimuli, and stress can alter the brain response to gut stimuli. This effect is both through central modulation of afferent gut stimuli and decreased efferent inhibition of pain signals [57, 58].

Though the brain is the most likely level for psychological input to interface with visceral input, very few studies have investigated the role of psychological factors in modulating the central nervous system response to visceral sensations. Berman and colleagues studied anticipation of visceral pain [59]. They found that negative affect reduces anticipatory brain stem inhibition. Reduced anticipatory brain stem inhibition in turn was associated with increased brain responsiveness to actual distention [59]. Ringel and colleagues observed that during rectal distension, patients with IBS and abuse history show greater posterior/middle dorsal and anterior cingulate cortex activation, as well as reduced activity of the supragenual anterior cingulate (a region implicated in pain inhibition and arousal) [60, 61]. Gupta and colleagues reported increased connectivity in the left putamen and decreased connectivity in the supplementary motor area, insular, anterior cingulate cortex, parietal, and frontal regions in IBS patients with a history of early adverse life events [62]. This suggests that early life events may potentiate changes in the brain salience network resulting in increased attention/behavior toward gut sensations. In a case report of a patient with severe IBS and post-traumatic stress disorder, resolution of emotional distress was associated with reduction in activation of the midcingulate cortex, prefrontal area 6/44, and the somatosensory cortex areas associated with pain intensity encoding [63]. Thus, there is evidence that psychological factors can influence brain reactions to visceral pain, specifically areas related to emotion modulation and attention control, but the exact mechanism still needs to be determined.

Stress and Gastrointestinal Inflammation, Gut Barrier Functioning, and Gut Microbiome

The role of the immune system in functional gastrointestinal and motility disorders, specifically IBS, initially focused on patients who developed IBS following an infectious gastroenteritis. Interestingly, stress around the time of the infection is one of the most robust predictors to develop post-infectious IBS. Later, low-grade inflammation within the gut wall as well as altered immunological function and alterations in gut flora were found in functional gastrointestinal disorders of noninfectious origin including IBS, functional dyspepsia, and noncardiac chest pain [64–66]. Many innate and adaptive immune parameters have been studied, but among the most robust findings are increased levels of mast cells, monocytes, and T-cells as well as increased intestinal permeability (for a review, see Ohman and Simren [67]). Although most studies have been done in adults, increased gut inflammation has also been shown in children who suffer from functional abdominal pain [68–71]. Gut inflammation in IBS is modest and subclinical as most patients have normal or near-normal fecal calprotectin concentrations [68, 72–74]. Nowadays, the role of the microbiota is being studied as contributing to gut inflammation. Dysbiosis of the microbiota has been found in IBS [75–78] and may also play a role in infant colic [79, 80]. Furthermore, probiotics are efficacious in reducing IBS and colic symptoms [81, 82]. The role of the microbiota is considered so central to the disorder that some have proposed to broaden the traditional brain-gut axis to include the microbiota: a brain-gut-microbiota axis [83].

There are many studies which suggest that psychological distress affects the immune system in healthy adults (for a meta-analysis see Denson et al. [84]). For example, stress reduces antigens production following vaccinations [85, 86] and increases susceptibility to colds [87], and meditation decreases IL-6 responses to a laboratory psychosocial stressor [88]. The role of stress on the immune system in functional gastrointestinal and motility disorders has received little attention. In rats and rodents, stress increased low-grade inflammation in the gut [89, 90, 91] as well as esophageal and intestinal permeability [92]. Inhibition of cytokines, such as Il-6, normalized stress-induced defecation, suggesting that immune and stress interactions are important in predicting stress-induced IBS symptoms [93]. Studies in humans also suggest that stress is associated with low-grade inflammation in functional gastrointestinal disorders. Depression and anxiety scores in IBS patients are correlated with increased mast cells [71, 94]. How close these mast cells are to gut nerves was also associated with ratings of stress and depression [95]. Stress has been associated with increased Il-6 levels in IBS patients [96, 97]. Anxiety has been reported to be associated with increases in cytokine levels in IBS but only after exposure to *Escherichia coli* lipopolysaccharides [98]. A recent study found that early-life stress in IBS patients was associated with brain changes in areas of mood and effect and inflammatory genes [99]. Stress also increases intestinal permeability in healthy volunteers [100].

These are indicators that stress and the immune system interact in functional gastrointestinal and motility disorders. Psychological distress may affect immunological response and reducing stress could be helpful. But there is also data to suggest that immune activation may *drive* psychological distress and brain-related changes. Activation of the immune system either by viral infection or by administration of

cytokines or lipopolysaccharide (found on the outer membrane of gram-negative bacteria) induces cytokine secretion and triggers depression and anxiety in healthy volunteers [101, 102]. In addition, immune-targeted therapies such as interferon-alpha treatment for Hepatitis C or cancer have been known to induce anxiety and depression in a significant percentage of patients [103–105]. Those who develop major depression during treatment have increased pretreatment IL-6 and IL-10 concentrations [106]. These findings suggest that that increased immune activation is a causal risk for the development of major depression. Based on these observations, Goehler et al. [107] have suggested that "Some of the negative affective experiences associated with gastrointestinal disorders may not be under the voluntary control of the patient."

Although it yet has to be determined how infections in the gut influence the brain and mood, it has been suggested that the brain may react directly to the bacterial composition of the GI tract [107, 108]. The gut contains different species of microbiota, many of which still need to be characterized. Imbalances in gastrointestinal microbiota, or "dysbiosis," have been found in many chronic gastrointestinal disorders such as IBD [109], antibiotic-induced diarrhea [110, 111], IBS [75, 83], and infant colic [79, 80]. Inducing dysbiosis, either with the use of oral antibiotics or by replacing the microbiota, leads to low-grade inflammation, visceral hyperalgesia, and behavioral changes in mice, symptoms changes that are also characteristic of many functional gastrointestinal disorders [112–114]. Furthermore, treatments that change the microbiota such as rifaximin and probiotics have been found to improve functional gastrointestinal symptoms [75, 82, 83].

A hypothesized model of how gut microbiota dysbiosis can influence the brain is through regulating intestinal barrier function resulting in increased gut permeability [115]. This could potentially allow antigens or pathogens to enter intestinal tissues and generate an inflammatory reaction. The resulting circulating cytokines are proposed to bind to brain endothelial cells, increasing the permeability of the blood-brain barrier and enhancing infiltration of immune parameters in the brain, which may cause or exacerbate mood/behaviors [116]. This pathway is largely untested, but studies have found increased gut permeability and immune activation among children with IBS [68, 117, 118] as well as changes in the microbiota in stressed individuals [116]; both of these findings are supportive of the suggested model. On the other hand, stress may alter gastrointestinal motility (as discussed previously) or induce changes in diet, which can modify the microbiota, suggesting a bidirectional association between stress and microbiota.

There is large evidence of immune-microbiota interactions suggesting the effect of dysbiosis on gastrointestinal symptoms is through the immune system [119]. However, the interaction of stress with gastrointestinal symptoms may also be through the vagus nerve. The vagal nerve has been implicated both in neurological control of the immune system particularly cytokine control [120] and in dysregulation of the brain-gut interactions in functional gastrointestinal disorders [121]. Vagal sensory neurons react to potentially dangerous bacteria in the GI tract independently of an immunological reaction to their presence: it has been reported that the vagal nerve is stimulated hours before bacteria are able to colonize [122, 123]. In fact, mice with dysbiosis show anxiety-like behavior in the absence of circulating pro-inflammatory cytokines and classic sickness behaviors [122], and in IBS patients, no association is found between cytokines and vagal tone [124]. In addition, administration of probiotics reduced anxiety-like behavior in mice with colitis, but only if they had an intact vagus nerve [114]. Thus, the vagal nerve can provide signal to the brain on dysbiosis before inflammatory responses reach the brain through the systemic circulation. Goehler argues that the adaptive value of enhanced anxiety during gut infection may lay in threat avoidance [107]. Behavioral responses to an infection, such as psychomotor retardation, may leave an animal vulnerable to predators. Avoidance of dangerous situations such as open spaces is essential and accomplished by early inducement of anxiety to stimulate threat avoidance. This will put the animal in less danger once sickness behaviors are full blown. Given that even low-grade inflammation can induce alterations in mood, this may be partially responsible for increased anxiety and depression in functional gastrointestinal disorders.

Conclusion

There is clear evidence that psychosocial factors can alter gut physiology important to functional gastrointestinal disorders such as effects on motility, visceral sensitivity, immune activity, and gut barrier functioning. The vagus nerve, CRF, and microbiota play important mechanistic roles in stress-related changes of gut functioning. Some evidence is available that gut-brain interactions are bidirectional, meaning that gut dysfunctioning can also influence mood. The gut affects mood through similar pathways such as the vagus nerve and microbiota.

One caveat to the above line of research is the almost exclusive focus on a single disease entity: IBS. More research is needed in other functional gastrointestinal disorders to determine if the bidirectional interactions of stress and gut physiology are general to a larger group of patients and disorders. In addition, pediatrics studies are largely lacking. Childhood offers a unique psychosocial environment embedded within different stages of psychosocial and physiological development. Studying these factors would add an extra dimension to the current literature. For example, we know

very little about the psychosocial influences on our youngest patients: those with infant regurgitation or toddler's diarrhea and how early colonization of the gut may be affected by stress. More research is needed to guide our understanding of psychosocial factors in childhood functional gastrointestinal and motility disorders.

In summary, in order to thoroughly understand functional gastrointestinal and motility disorders, it is important to look beyond the biomedical causes of these disorders and to consider personal and social factors that influence the symptom report of patients. Clearly, psychosocial factors play a role not only in gut physiology but also in symptom perception and illness behaviors as well. Children with similar symptoms may show very differential outcomes depending on their psychosocial profile [125, 126]. The child with good coping skills and low anxiety will likely improve quickly, while the child who is anxious, has poor coping skills, experiences a multitude of stressful life events, and has feelings of low self-worth is more likely to continue to suffer from pain and impairment. Johnny—our case from the beginning of this chapter—was not helped by exclusively treating the biological factors that were driving his symptoms. He needed an integrated treatment approach that consisted of improving delayed gastric emptying (physiological factor) as well as helping him overcome his fear of eating (personal factor) and his mother's anxiety (social factor). Symptoms in children with functional gastrointestinal disorders result from an interplay among biomedical causes and many possible psychosocial factors such as anxiety, depression, hypervigilance to symptoms, inadequate coping, the way parents respond to their pain, bullying, unsanitary toilets at school, and many more.

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Part II

Motility and Sensory Testing

Esophageal Manometry

7

Rossella Turco and Annamaria Staiano

Esophageal manometry has been considered the "gold standard" test for the evaluation of esophageal motor function. Esophageal manometry allows the physician to assess peristalsis by measuring the shape, amplitude, and duration of the esophageal contractions [1]. The clinical use of esophageal manometry is in defining the contractile characteristics of the esophagus in an attempt to identify pathological conditions. Esophageal manometry is performed differently in children than in adults because of the differences in size of the esophagus, cooperation by the patient, and neurologic and developmental maturation. These differences require special equipment as well as technical expertise to perform the study, handle the patient, and properly interpret the findings [2].

Normal Motility

The esophagus acts as a conduit for the aboral transport of food from the mouth to the stomach. The three structural components of the esophagus are the upper esophageal sphincter (UES), the esophageal body, and the lower esophageal sphincter (LES) [3]. The UES is physiologically defined as a zone of high intraluminal pressure between the pharynx and the cervical esophagus, which comprises the functional activity of three adjacent striated muscles, creating a tonically closed valve and preventing air from entering into the gastrointestinal tract. The main functions of the UES are to provide the most proximal physical barrier of the gastrointestinal (GI) tract against pharyngeal and laryngeal reflux during esophageal peristalsis and to avoid the entry of air into the digestive tract during negative intrathoracic pressure events, such as inspiration. The UES relaxes both transiently during swallowing, in order to allow the entry of a bolus into the esophagus, and during belching and vomiting, in order to allow the egress of gastric contents from the esophageal lumen. The UES is present by at least 32 weeks of gestation and is functional at birth [4]. However, swallowing coordination may be poor in the first week of life and in premature infants <1500 g [5, 6]. Structurally, the UES is ~0.5–1 cm long at birth and increases in length to ~3 cm in the adult [3].

The LES is the high pressure zone composed entirely of smooth muscle which maintains a steady baseline tone to prevent retrograde movement of gastric content into the esophagus. During swallowing and belching, the LES promptly relaxes in order to allow the passage of ingested food or air in appropriate directions. 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. This relaxation starts within 2 s after the peristaltic contraction has begun in the 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 propelled by the peristaltic wave. The LES relaxation is followed by an after-contraction of the upper part of sphincter, which likely represents the end of contraction wave as it reaches the distal esophagus. Swallow-induced LES relaxation is part of primary peristalsis. Like the UES, LES length increases with age, from 1 cm in the newborn to 2–4 cm in the adult. LES pressure also varies with age, going from 7 mmHg in a premature infant of 27 weeks gestation to 18 mmHg at term and from 10 to 45 mmHg in adults [7, 8].

The body of the esophagus is similarly composed of two muscle types. The proximal esophagus is a predominantly striated muscle, while the distal esophagus and the remainder of the GI tract are composed of smooth muscle. The mid-esophagus contains a graded transition of striated and smooth muscle types. The muscle is oriented in two perpendicular opposing layers: an inner circular layer and an outer longitu-

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dinal layer, known collectively as the muscularis propria. The longitudinal muscle is responsible for shortening the esophagus, while the circular muscle forms lumen-occluding ring contractions.

The muscle layers contract simultaneously and produce peristalsis. Peristalsis is a sequential, coordinated contraction wave that travels the entire length of the esophagus, propelling intraluminal contents distally to the stomach. The LES relaxes during swallows and stays opened until the peristaltic wave travels through the LES and then contracts and redevelops resting basal tone. Peristalsis is divided in three phases.

The primary peristalsis is the peristaltic wave triggered by the swallowing center. The peristaltic contraction wave travels at a speed of 2 cm/s and correlates with manometry-recorded contractions. The secondary peristaltic wave is induced by esophageal distension from the retained bolus, refluxed material, or swallowed air. The primary role is to clear the esophagus of retained food or any gastroesophageal refluxes. The tertiary contractions are simultaneous, isolated, and dysfunctional contractions. These contractions are non-peristaltic, have no known physiologic role, and are observed with increased frequency in elderly people.

Technical Aspects

High-resolution manometry (HRM) was developed to increase interpretative consistency and diagnostic accuracy of esophageal manometry [9, 10]. In contrast to conventional manometry, HRM has two minimum requirements that improve spatiotemporal resolution: recording sites that are positioned closely enough (usually at 1 cm intervals) to allow accurate interpolation of data between sites and an appropriate computer system for acquisition of the data and creation of the desired three-dimensional plots [9]. Axial interpolation has already proved useful in understanding the correct relationship of pressure data when unusual wave forms occur, for example, multi-peaked waves [10]. Three-dimensional topographical plots are convenient methods of visually representing the large amount of data provided by the increased number of recording sites (Fig. 7.1).

On a theoretical level, HRM provides advantages over conventional techniques for the assessment of esophageal function. One of the most important advantages of HRM is that it makes diagnostic esophageal manometry easier and quicker to perform. It takes away the need for a pull-through and precise positioning of the manometric catheter with respect to the LES. A lab technician or nurse can thus simply perform HRM, and only limited experience in esophageal manometry is required. The pattern of esophageal peristalsis and sphincter activity defines whether esophageal motor activity is normal or abnormal. The intrabolus pressure and esophagogastric pressure gradient define whether or not this activity is consistent with effective function. On a practical level, HRM makes it easy to acquire good quality pressure measurements from the esophagus, facilitates positioning of the catheter, and removes the need for a pull-through procedure. Moreover, spatiotemporal plots of pressure information make it easy to identify normal and abnormal patterns of esophageal motility [11].

A manometric apparatus consists of a pressure sensors and transducers combination, which detects the intraluminal pressure and changes it into an electrical signal, and a recording device to amplify, record, and store that electrical signal. Although each component can potentially affect recording fidelity, most attention is rightfully focused on the pressure sensor and transducer combination. Recorders (whether they are ink-writing polygraphs, thermal writing polygraphs, or computers with analogue to digital converters) all possess response characteristics far in excess of that required for recording esophageal pressure complexes.

Three types of data display can be generated and are available for review immediately after completion of the recording sessions, each taking into consideration both time and space relationships of manometric data. Surface plots are three-dimensional representations examined from different elevations or perspectives; contour plots represent three-dimensional data in a single "overhead" perspective as is commonly used to display geographic or weather data; and axial transformations represent data at a single time across all of the recording channels, the dimension of time being represented by an animation of the data frames. In all cases, the initial step involves alignment of the manometric data on a planar surface [9].

The *surface plots* are created by exporting three-dimensional data sets to a program specifically designed for geographic mapping. The developed system creates x, y, z data sets for specified time intervals following designated event markers inserted during analysis. For these data sets, x represents the recording site position on the catheter in cm, y the time after the event marker in seconds, and z the pressure amplitude at that time and location in mmHg. In creating surface plots, a grid of data is first established, the gridline interval being determined by the investigator for both the x and y directions. For the purposes of esophageal plotting, gridlines are usually positioned at 0.2 cm and 0.2 s intervals. The z value (pressure amplitude) is interpolated at each grid intersection using available neighboring data for establishing the most appropriate value. Resultant plots can be tilted forward or rotated as required to best visualize the three-dimensional data [9]. *Contour plots* represent an overhead perspective of surface plots, each contour ring encircling amplitudes of equal or greater value than that specified on the color legend. A series of concentric rings indicates a regional pressure peak on the plot. In the developed system,

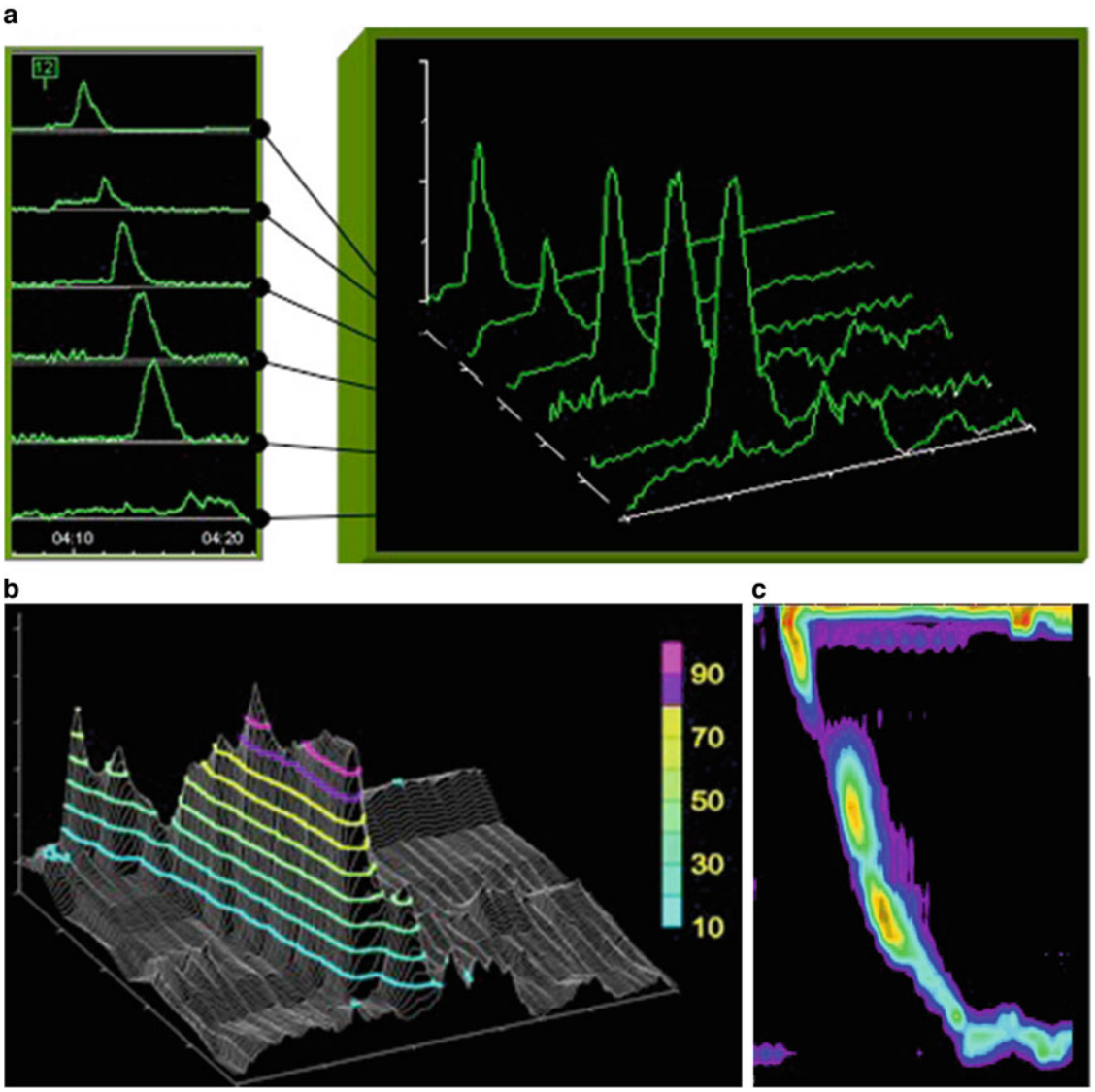

Fig. 7.1 High-resolution manometry. (**a**) Tracings are aligned on a planar surface so that spatial relationships of pressure data between recording sensors can be established. (**b**) Interpolation of pressure data between sensors is performed, and colors are applied to pressure levels according to a scale. (**c**) Overhead "contour maps" reveals the segmental nature of esophageal peristalsis

the plot baseline can be shifted as required for zero adjustment (e.g., to match intragastric pressure). Likewise, the first contour level as well as the pressure interval for subsequent rings can be modified as required. The *axial transformations* of manometric data are available only on the developed system. Individual frames are created by splining data across all recording sites at a specified time following an inserted or adjusted event marker. All frames are then viewed as an animated movie, the animation speed adjusted by the investigator (Figs. 7.1 and 7.2) [9].

Two basic varieties of manometric systems (water-perfused and solid-state systems) are now available to perform HRM. Each design has distinct advantages and disadvantages.

The water-perfused catheters for HRM with 21–32 channels and, more recently, up to 36 pressure sensors contain smaller lumina, which are perfused at very low rates. In children, at least 80 % of the esophageal body and one sphincter could be sampled with the catheter with 21 lm in either a proximal or distal recording position. With this design, a 20 cm segment is sampled simultaneously. Data acquired by HRM can be analyzed and presented either as multiple line plots or as a spatiotemporal plot. In water-perfused systems, pressures are transmitted along a column of water to external transducers. This makes the catheters more flexible and cheaper but more unwieldy to use as the water perfusion pump must be set up and the dynamic fidelity of the system is damped by the compliance of the water perfusion system.

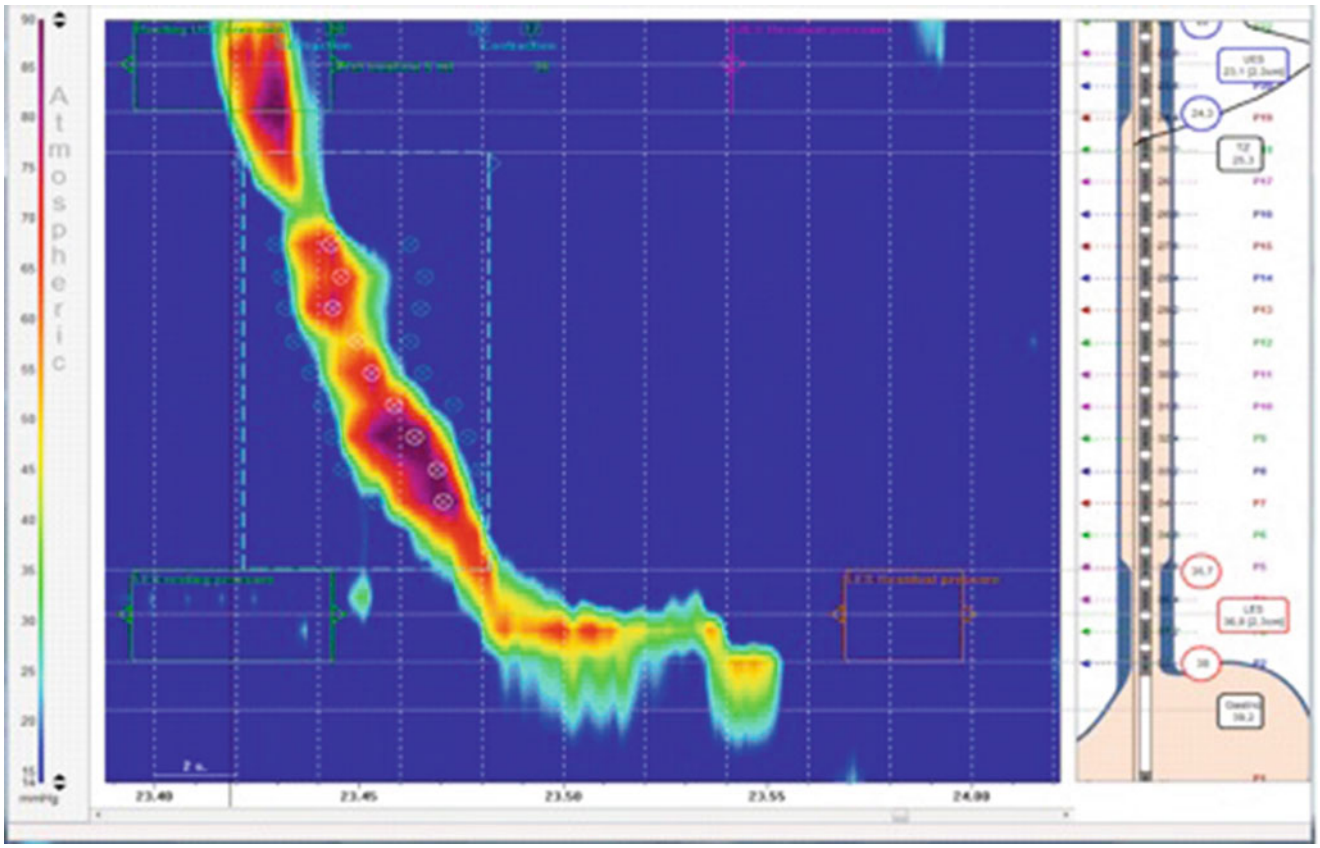

Fig. 7.2 A complete peristaltic chain is seen in this image. The segmental pressure architecture resembles what is seen in the healthy adult. The three intersegmental troughs are indicated on the figure, and the pressure amplitudes represented by the isobaric contour regions are shown in the color legend (in mmHg above gastric baseline pressure; pressures below the first isobaric contour are shown in *dark blue*)

With water-perfused systems, a pneumohydraulic pump perfuses distilled water through the lumens of the multilumen manometric catheter. Each lumen is connected to an external volume displacement pressure transducer and terminates at a side-hole or sleeve channel within the esophagus, sensing the intraluminal pressure at that position by the relative obstruction to the flow of the perfusate. In addition to having well-defined, time-tested response characteristics, other advantages of the perfused manometric system are: 1) low cost; 2) easy availability of 8 lm extruded polyvinyl tubes that can be made into manometric assemblies of varied sensor configuration; 3) compatibility with sleeve devices for assessing sphincter function, and 4) temperature stability. Disadvantages of perfused manometric systems are as follows: 1) Proper equipment maintenance, which is essential for the system to achieve published response characteristics, requires relatively skilled personnel; 2) recording characteristics are unsuitable for accurate pharyngeal studies [7].

Differently from water-perfused system, in the solid-state system, the pressure transducers are incorporated into the catheter itself. This makes the pressure rise rate high, particularly where pressure changes are rapid (e.g., the pharynx).

The main alternative to the water-perfused manometric system is a manometric assembly incorporating strain gauge sensors and solid-state electronic elements. In these manometric systems, the manometric probe contains the transducers at fixed locations along its length. The probe plugs into a small box containing the electronic elements, connected to the recorder. The advantages of intraluminal strain gauge systems are their vastly expanded frequency response, making them suitable for recording any intraluminal pressure activity, and their less cumbersome nature compared with perfusion pumps, requiring less skilled personnel to perform clinical studies and less equipment maintenance. The main disadvantages are as follows: the manometric probes are expensive, sometimes fragile, and unmodifiable; manometric probes are subject to several physical constraints with respect to the number of sensing elements and the proximity of the elements to each other; and there is no equivalent of a sleeve device compatible with this system [7].

With either system, the spacing of the sensing ports depends on the size of the patient. The interval between perfusion ports or transducers may need to be as close as 1–3 cm apart to accommodate the shorter esophagus in infants.

During perfusion in infants and small children, the perfusion rate may need to be lower because of the size of the esophagus, the fluid tolerance of infants, and the potential for aspiration. Care must be exercised to compensate for the slower flow rate by decreasing the system compliance [2].

Methodological/Practical Aspects

Because of the differences in size of the esophagus, cooperation by the patient, and neurologic and developmental maturation, HRM is performed differently in children than in adults.

Esophageal HRM is best performed without sedation. In many children, however, sedation is necessary. Midazolam and chloral hydrate have been shown to be effective with minimal or no influence on pressure measurements [12, 13]. A natural reflex swallow may be induced in young infants and neurologically abnormal children by gently blowing in the child's face (Santmyer swallow) [14].

The single most difficult technical aspect of esophageal manometry in children is cooperation. Physicians performing manometry in children must have great patience, and the study needs to be performed by experienced staff and a supportive parent/guardian. The patient's cooperation can, however, be improved by the use of age-appropriate relaxation techniques. For example, infants relax with swaddling and use of a pacifier. Toddlers are comforted having a favorite blanket or toy. School-age children benefit from being allowed to handle and examine equipment before the procedure. Adolescents benefit from a thorough review of what to expect before the procedure. Recording artifacts are common in the pediatric patient and occur more commonly than in adults. Specific behaviors (e.g., crying or squirming) should be noted on the tracing itself to allow proper interpretation upon completion of the study [2].

Catheter size has a significant impact on tolerance. Currently standard HRM catheter size is 12.5 French, and with this catheter size we would be very reluctant to perform a study in a child under 7 kg. Once the catheter is in position, children will usually (within 5–10 min) become accustomed to the catheter. However, they may resist swallowing of boluses or may not swallow on command particularly if cognitively impaired. When children do not swallow on command, techniques such as cervical auscultation or palpation of the throat can be used to assist in marking the primary swallow. A natural reflex swallow may be induced in young infants and neurologically abnormal children by gently blowing in the child's face.

The following protocol is recommended:

- Position the catheter across the EGJ using standard landmarks.
- Perform baseline recording of LES pressure, allowing for an initial 3 min "settling down" period.
- Administer wet swallows (10 swallows at a minimum of 20 s intervals of 0.5–5.0 mL, aiming for the maximal tolerated volume, 5 mL for those older than 5 years of age, 2 mL for those under 5 years, and 0.5–1 mL for infants), and consider wet swallows unsafe in patients with oropharyngeal dysphagia.
- Check multiple rapid swallows offering about 100 mL of liquid by means of a straw or a bottle.
- Consider solid swallows of the patient has symptoms triggered by the consumption of solid food.

Analysis

Despite the technical advances, considerable time and expertise are required to obtain a technically adequate and maximally informative study of esophageal function by this technique. At present, abnormal motor activity as measured by "conventional manometry" is defined in terms of a few basic patterns: incomplete sphincter relaxation, esophageal spasm, hypertensive contractions, and loss of tone and motility [11, 15, 16]. This classification is simple; however, even for experienced physiologists in specialist centers, interobserver agreement in the interpretation of manometric measurements is poor [17]. Only achalasia and severe diffuse esophageal spasm are specific disorders with manometric abnormalities that are absent in healthy subjects. Other esophageal motility disorders are poorly defined, often include "abnormalities" that can be found in symptom-free individuals as well [18, 19] and are inconsistent over time [20].

One important observation made in adults that accentuates the value of HRM is that esophageal peristalsis is comprised of a specific chain of sequential pressure segments (Fig. 7.2). These segments, one in the striated muscle region and two in the smooth muscle region, appear as concentrated pressure loci separated from each other by lower amplitude pressure troughs on the three-dimensional maps [21–25].

Staiano et al. reported that the same chain of pressure segments identified previously in adults was recognized in every child with the exception of seven with aperistalsis, six of whom were ultimately diagnosed as having achalasia [22]. The first and second pressure troughs were similarly distributed across esophageal length in each age group, but the third trough was located proportionately less closely to the upper margin of the resting LES in the neonates compared with infants/toddlers or children [22]. The first pressure segment was more consistently present in children than in the other two age groups, and the percentage of swallows with the third pressure trough was decreased in neonates compared with children. Consequently, completely formed peristaltic chains

were less commonly observed in the neonates, but the number of subjects was too small to confirm that this was a clinically meaningful finding [22]. No differences were found in the presence or distribution of the pressure segments within the esophageal body in subjects who had symptoms ultimately attributed to esophageal disease or who had other explanations for the presenting complaints.

Staiano et al. have demonstrated in an HRM study of healthy preterm and term neonates that maturation of the peristaltic chain continues to occur through late gestation and beyond term birth. The same segmental architecture of peristalsis was observed in term and preterm neonates as reported previously in children and adults, and no additional pressure segments or troughs were identified by subjective review of the maps. It was suggested that maturation may continue through the infant/toddler period such that presence of the complete peristaltic chain at rates matching the adult pattern only becomes most evident during childhood years [26].

Although the three contraction segments could be identified in each age subgroup (neonates, infants/toddlers, children), the percentage of complete peristaltic chains appeared reduced in the very small number of neonates studied. The segmental architecture was distinctive for each infant such that identifying peristaltic sequences was simple using high-resolution manometric techniques. The second and third segments overlapped in the distal esophagus as they do in adults [10] such that part of the segment would extend into the neighboring region, yet a set of concentric isobaric contour lines focused on the region (the defining characteristics of a segment) was absent. The first and third segments were present in ≥50 % of swallows in very few of the preterm neonates and in a significantly larger proportion of full-term neonates. In contrast, the second segment was well developed in ≥50 % of swallows in all preterm and full-term neonates, even in the youngest of studied subjects [26]. These findings indicate that the second segment develops early and is most consistently present, even in preterm neonates. This segment may have particular value in esophageal clearance [27], its early development, thus being of teleologic importance [26]. In addition, the authors demonstrated that although all the segments can be identified in infants as young as 27 weeks of gestational age at the time of examination, the consistency of their presence continues to increase through the normal gestational period. At full term, only 55 % of swallows have a complete segmental chain, indicating that further development occurs in early infancy. These results support a potential role of inadequate esophageal body motor function in the presentation or manifestations of GERD in infants [26].

Recently, Goldani et al. have illustrated the use of HRM in a pediatric age group while using a standardized protocol and analytical method. Despite the inherent limitations of the pediatric population, the authors introduced a new protocol in un-sedated children in the context of a clinical setting, moving from research into clinical application. The ability to analyze data using spatiotemporal plots normalized to gastric baseline pressure eliminates a great deal of motion artifacts, which previously required many children to be sedated for the procedure [28]. The additional use of solid swallow has been described in adults to diagnose esophageal spasm in patients with dysphagia who underwent normal conventional manometry [29]. Goldani et al. were the first to describe the usefulness of solid swallows in pediatric patients. Further studies are needed to determine normal patterns of esophageal solid bolus transit in children, given the finding that healthy adults may need more than one swallow to clear solid boluses from the esophagus and that subjects have poor perception of whether such boluses cleared the esophagus on any given swallow [30].

Goldani et al. introduced the new parameter DCIa, which may be useful for the assessment of hypotensive peristalsis in patients with peristaltic dysfunction. On the basis of all the evidence presented above, we advocate that children should ideally not be sedated for HRM and should adhere to the protocol above reported. This protocol is adapted from what is recommended in adults [11] and is expected to fit into the pediatric age. Conventional analytical methods and the new DCIa variable may be useful to further clarify paradigms regarding the pathophysiology of motility abnormalities and consequently improve the diagnosis of pediatric esophageal motility disorders [30].

Reference Values

It was inevitable that the introduction of esophageal pressure topography (EPT) led to new metrics and parameters of HRM. This strengthened the need to reassess the classification scheme, which was originally developed for conventional manometry measurements. In 2008, the first official classification system for EPT, the Chicago classification (CC), was developed after several studies in healthy volunteers and patients [31–35]. The last updated of CC was made in 2015. CC, through the analysis of five EPT metrics based on ten liquid swallows, characterizes esophageal motility disorders in four main categories: achalasia (Category 1), esophagogastric junction (EGJ) outflow obstruction (Category 2), disorders never observed in healthy individuals (Category 3, absent peristalsis, diffuse esophageal spasm (DES), or hypercontractile esophagus), and motor patterns outside the normal range (Category 4, weak peristalsis, frequent failed peristalsis, hypertensive peristalsis, or rapid contraction).

The standard EPT metrics derived are (1) integrated relaxation pressure (IRP4s), (2) contractile front velocity (CFV, cm/s), (3) distal contractile integral (DCI, mmHg

cm/s), (4) distal latency (DL, s), and (5) peristaltic 20 mmHg isocontour break size (BS, cm).

However, the applicability of CC in pediatric population is challenging. As a matter of fact, pediatric normative ranges for EPT metrics and some metrics are lacking. In particular it is possible that the shorter esophageal length and the smaller lumen diameter can influence the EPT metrics. Due to these differences with adults, Goldani et al. proposed adjustment of the DCI for esophageal length, in pediatric age [28]. A recent systematic analysis of a large series of clinical EPT studies in a pediatric cohort tried to adjust the diagnostic CC criteria for esophageal motility disorders according to age and size. Authors demonstrated that certain EPT metrics are substantially influenced by age/size and that this can change the diagnosis. The most important is represented by an increase in the IRP4s and the shortening of DL in the younger/smaller patients which may lead to an overdiagnosis of EGJ outflow obstruction or DES. Important EPT metrics therefore require adjustment to reduce the possibility of overdiagnosis of Category 2 and 3 disorders and underdiagnosis of Category 4 disorders in pediatric patients. Another recent paper showed that automated software-based CC diagnosis of pediatric esophageal motility disorders had high inter- and intra-rater reliability of the CC among experts and nonexperts, while the semiautomated analysis is least reliable especially for the diagnosis of disorders such as DES and achalasia.

Indications

Principal recommendations of esophageal HRM are as follows:

- Evaluation of symptoms or signs of esophageal dysfunction, such as dysphagia, odynophagia, not cardiogenic chest pain, aspiration, and recurrent food impaction
- Evaluation of connective tissue diseases
- Evaluation of outcomes after caustic ingestion
- Diagnosis of achalasia (Fig. 7.3) and post-surgery evaluation of patient with achalasia still symptomatic
- Evaluation of patients with gastroesophageal reflux, to exclude primary disorders of esophageal motility
- Evaluation of patients undergoing anti-reflux surgery, to exclude primary disorders of esophageal motility
- Evaluation of recurrent nausea and vomiting, to exclude rumination syndrome

The advantages of esophageal HRM have been described in a series of recent publications [36]. Closely spaced pressure channels provide detailed pressure information that reveals the segmental nature of esophageal peristalsis. This is important because motor abnormalities can be limited to a short segment of the esophagus and will be missed by pressure sensors spaced too far apart [21, 37]. HRM increases the accuracy by which bolus transport can be predicted from manometry [37]. This is significant because abnormal bolus transport is a more important cause of esophageal symptoms than manometric abnormalities per se [38]. Esophageal HRM identifies patients with poor coordination between the proximal and mid-esophagus (wide "transition zone"), focal hypotensive contractions or focal spasm that would be missed by conventional manometry. Crucially, HRM can distinguish between abnormalities that disturb bolus transport from abnormalities that have no effect on function (i.e., improves sensitivity *and* specificity of manometric investigation) [37]. The measurement of pressure gradients within the esophageal body and across the gastroesophageal junction (GEJ) provides an objective assessment of the forces that direct bolus transport [33]. The clinical importance of this is illustrated by the finding that the pressure gradient across the GEJ has higher accuracy for the diagnosis of achalasia than conventional measurements of sphincter relaxation (Fig. 7.3) [39]. HRM has been shown to increase diagnostic accuracy. In a group of 212 unselected adult patients, Clouse et al. reported manometric disagreement in 12% between HRM and conventional manometry. Compared against "final diagnosis" 6 months after the investigation, conventional manometry failed to identify several patients with achalasia and other causes of hypotensive and aperistaltic motility disorders, while the topographical method correctly identified all patients with achalasia within the group with aperistalsis. They concluded that the topographical methods are more accurate than traditional techniques in diagnosing the type of severe motor dysfunction and provide additional information important in the clinical practice of esophageal manometry [40].

Published case series supply vivid examples of clinically important pathology detected by esophageal HRM that was not provided (or not properly appreciated) by conventional investigation:

1. The loss of coordination (wide "transition zone") between the proximal (striated) and mid-distal (smooth muscle) esophagus.
2. Focal esophageal spasm limited to the mid-esophagus.
3. Detection of an abnormal pressure gradient (i.e., resistance to flow) localizes pathology within the pharynx and UES (e.g., cricopharyngeal bar) [41].
4. Functional (e.g., achalasia) resistance to bolus transport across the GEJ can be measured and pseudo-relaxation of the LES in vigorous achalasia is clearly seen.
5. Structural resistance to bolus transport caused by peptic stricture, extrinsic compression can be identified on HRM. This ability to differentiate the functional and

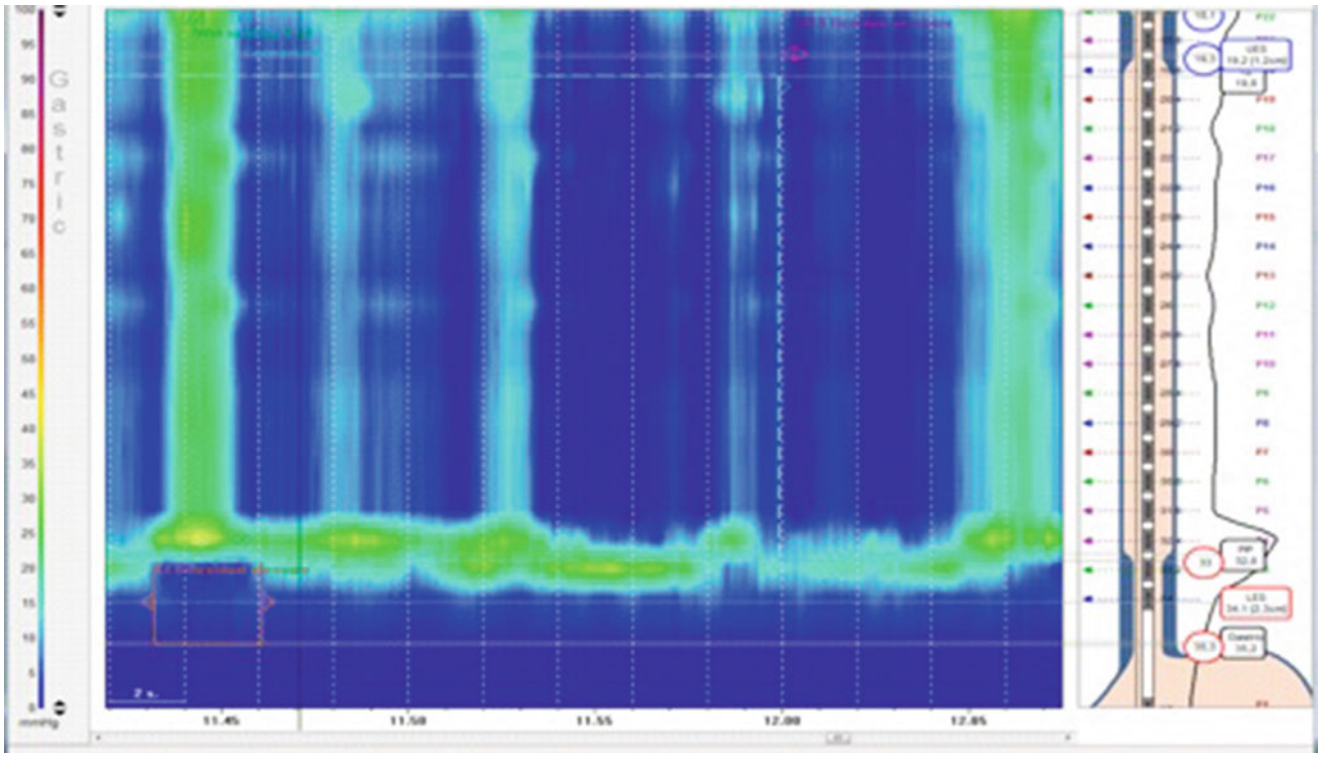

Fig. 7.3 Peristaltic segments are absent in this child with achalasia. The peristaltic chain is replaced by isobaric contour stripes spanning the esophageal body

structural anatomy of the GEJ greatly improves the ability to identify problems post-fundoplication [37].

Esophageal dysmotility is frequent in children suffering from esophageal atresia (EA) and tracheoesophageal fistula and frequently is associated with gastroesophageal reflux (GER). The incidence of GER varies from 41 % based on symptoms only [16] to 68 % measured by pH monitor, 72 % by barium swallow, and 65 % by scintiscan [40]. The dysmotility may be congenital. Cheng et al. reported a Chinese boy with achalasia, identified by the esophageal conventional manometry, associated with EA [43]. In adults, Dutta et al. reported that the pressure and contractility profile of the esophagus was abnormal in the majority of patients, even in the absence of symptoms [44]. In children, no data exist yet regarding the use of HRM in children treated for EA.

Gastroesophageal reflux, often severe and with respiratory complications, occurs with increased frequency among children with psychomotor retardation. It has been reported that GER occurs in up to 70–75 % of children with cerebral palsy [45]; however, the mechanisms underlying its occurrence in neurologically impaired children (NIC) are poorly understood. In neurologically normal adults and children, simultaneous esophageal manometry and pH monitoring have shown that GER is usually due to a transient LES relaxation; whereas other mechanisms, including reduced basal sphincter tone, account for a minority of reflux episodes [33–51]. Pensabene et al. reported that absent LES tone is the most common mechanism of reflux of gastric contents into the esophagus in a subgroup of NIC. Transient LES relaxation, the most common known event associated with acid reflux in healthy premature infants, as well as in older children and in adults, seems to be an uncommon mechanism in NIC with undetectable LES [52], but no data exist regarding the use of HRM in NIC.

Finally, HRM has facilitated in children the routine measurement and analysis of physiological parameters not normally appreciated during a conventional manometric evaluation. Although HRM study protocols and normative data are well established in adults [11, 29, 32], pediatric data are sparse. HRM is simple to use and easy to learn for those with a basic knowledge of conventional manometry. No sleeve sensor is required (an electronic "virtual sleeve" provides an identical recording if required), and it has several advantages over conventional esophageal manometry [37]. HRM may prove to have clinical advantages in pediatric patients as it has in adults, but further proof of its usefulness in these subjects will be required. Current limitations of HRM in pediatrics relate largely to the pneumohydraulic perfusion of a catheter having multiple microlumina and the need for fastidious maintenance of this system to ensure accurate recordings.

Recent development of a 36-sensor solid-state catheter having circumferential pressure transducers embedded along its length has eliminated water perfusion, allows sampling of the entire esophagus without catheter repositioning, and has simplified HRM in adults [22].

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Antroduodenal Manometry

8

Efstratios Saliakellis, Anna Rybak, Nikhil Thapar, and Osvaldo Borrelli

Antroduodenal manometry (ADM) is a diagnostic tool that provides both a qualitative and quantitative assessment of the foregut motor function by recording intraluminal pressure changes within the gastric antrum and the proximal small intestine. Specifically, such pressure readings provide a measure of coordination and contractile activity of the foregut. Since the first manometric recordings, methodological improvements have steadily occurred, progressing ADM manometry from a purely research technique to an investigation commonly performed in adults and children for definitive clinical purposes. A substantial development has been the ability of the recording equipment to digitize online manometric recordings so that the latter can be easily analyzed by computer programs. Although the test is still performed in highly specialized motility centers, ADM has provided an improved understanding of the pathophysiology of neuromuscular disorder of the stomach and small intestine.

Normal Motility

In healthy individuals, the primary function of the small intestine is the absorption of nutrients, and the motor pattern is programmed to promote this function by assuring timely propulsion of luminal contents and avoiding stasis or, conversely, rapid transit of luminal contents. Under physiologic conditions, the motor activity of the antrum and the small intestine is characterized by patterns of organized motor activity in the fasting and postprandial periods [1].

Fasting or interdigestive gastrointestinal motility comprises a sequence of three main components or phases with a combined total average duration of about 100 min (50–180 min), which together constitute the so-called migrating motor complex (MMC) (Fig. 8.1) [2, 3]. Phase III of the MMC, the most distinctive and well-studied pattern of gastrointestinal motor activity, is a characteristic burst of high-amplitude rhythmic contractions of at least 2 min duration occurring at the maximum frequency allowed by the underlying myoelectrical rhythm for a given segment of the gastrointestinal tract [4]. For instance, in the antrum the contractions occur at a rate of 2–3 per min, whereas in the proximal small bowel, this increases to 10–14 per min. In children, phase III may begin anywhere from the stomach to the ileum, but in about 70 %, it starts in the gastric antrum, 18 % in the proximal duodenum, 10 % in the distal duodenum, and 1 % in the proximal jejunum [2, 3]. Migration is a basic requisite of phase III activity, which usually propagates aborally over various lengths of the small intestine; however, only 50 % of these propagate beyond the middle jejunum, and only 10 % reach the distal ileum [5]. The duration of phase III progressively increases in the aboral direction ranging between 2–5 min in the duodenum and 10–20 min in the distal ileum [2, 6–8]. Conversely, the propagation velocity of phase III decreases from 5 to 10 cm/min in the proximal small bowel to about 0.5–1 cm/min in the distal ileum [1, 2, 7]. The average amplitude of single contractions is at least 40 mmHg in the antrum and 20 mmHg in the small intestine. Finally, the mean interval between episodes of phase III varies with age. It ranges between 25 and 45 min in newborn, approximately 60 min in children less than 2 years and 85–110 min in adolescent and adults [3, 8–12]. However, significant variation between subjects and within the same individuals may be seen [2, 13, 14]. Phase III activity is usually followed by quiescence or phase I, which is defined as

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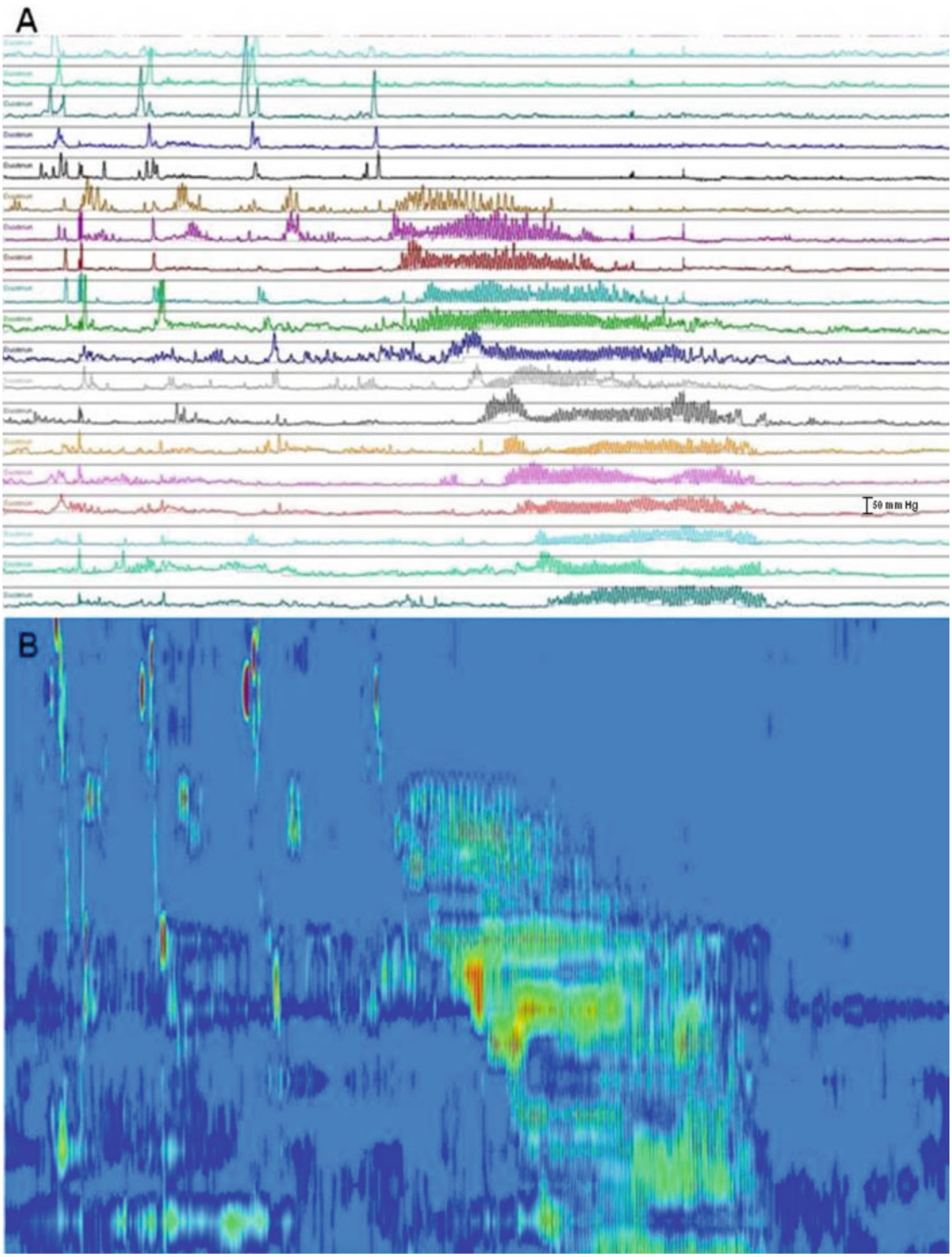

Fig. 8.1 Examples of conventional (**a**) and spatiotemporal plot (**b**) of normal migrating motor complex (MMC) recorded in a child with recurrent vomiting. All three phases (phase I, phase II, and phase III) are well represented. Phase III is seen starting in the duodenum and migrating aborally toward the proximal jejunum. A period of quiescence (phase I) follows phase III; the latter is preceded by intermittent phasic activity (phase II). Phase III is readily recognized by using spatiotemporal plots. The recording has been performed with a 20-channel manometric catheter (side holes 2.5 cm apart)

less than three pressure waves every 10 min [15]. Phase I is followed by a period (phase II) of irregular contractions (more than 3 pressure waves every 10 min), which represent in the small intestine about 70–80 % of the whole cycle. Phases I and III of the MMC require an intact enteric nervous system (ENS) with modulation by the central nervous system

and gastrointestinal regulatory peptides [5, 16, 17]. For instance, endogenous motilin blood concentration peaks during late phase II and phase III of the MMC cycle [18, 19]. However, motilin is not required for initiation or aboral migration of phase III in the small bowel, but seems to be involved in the antral participation of phase III [20, 21]. Conversely, phase II activity seems to rely more on extrinsic modulation of CNS, given it is suppressed during sleep and abolished after vagotomy [5, 16]. The importance of MMC is highlighted by the fact that its absence is associated with bacterial overgrowth [1]. Indeed, the pulsatile flow ahead of phase III is of paramount clinical importance for clearing secretion, debris, and microbes during the interdigestive period, whereas colonization of the foregut with gram-negative bacteria is observed when phase III is impaired or absent [22]. For this reason, phase III has been termed as the "gastrointestinal housekeeper." MMC cycles do not occur in the intestine of premature infants aged less than 34 weeks, which instead show a pattern of clustered phasic contractions lasting between 1 and 20 min and occurring every 4–35 min. As post-conceptional age increases, this activity becomes longer and the frequency of occurrences decreases. By term, well-defined cyclical fasting motor activity is present with distinct phase I, II, and III activity, with the latter showing less variability in terms of length and intervals [11, 23].

Following the ingestion of food, the MMC cycle is interrupted and replaced by a pattern of regular antral contractions associated with apparently uncoordinated contractions of variable amplitude in the small intestine, termed "postprandial" or "fed" pattern (Fig. 8.2) [5, 16, 24]. These phasic contractions also show variable frequency and propagation. Typical postprandial contractions usually propagate over a shorter distance than those of phase III, and almost 80 % of them propagate less than 2 cm [24]. This minute movement of postprandial contractions is devoted to mixing and grinding of the nutrient chyme, stirring, spreading and exposing the intestinal contents to a larger surface, and thus promoting its optimal absorption. Moreover, minute aboral transport is also sufficient in preventing bacterial colonization. Thus, normal postprandial motor activity is a compromise between optimal absorption and adequate clearance. The postprandial period lasts from the time of the evident increase in frequency and/or amplitude of contractions occurring after the introduction of a meal to the onset of the following phase III and is affected by the amount of calories as well as by the composition of the meal [25]. For instance, fats induce a more prolonged fed pattern than protein and carbohydrates. Extrinsic neural control is a prerequisite for a normal postprandial pattern, since persisting MMC activity after meal intake has been reported after vagal cooling [26, 27]. Neural reflex, endocrine, and paracrine mechanisms also play a key role [17]. In small infants aged less than 32 weeks post-conceptional age, who usually receive only small volumes of enteral feeding, the fasting pattern is not disrupted by either the bolus or continuous feeding. Between 31 and 35 weeks post-conceptional age, the larger volumes of enteral feeding induce a degree of postprandial activity, but it is only

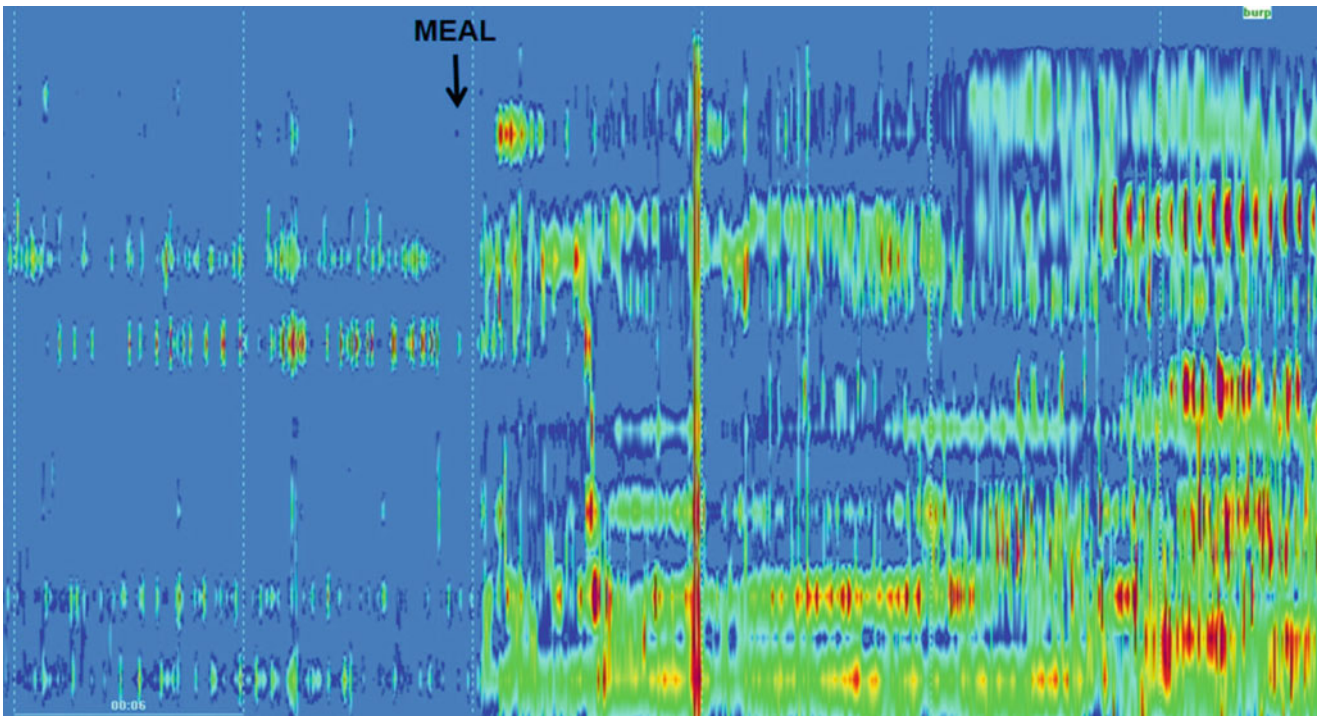

Fig. 8.2 Examples of spatiotemporal plot of normal postprandial activity characterized by irregular but persistent phasic activity. Temporal and pressure resolution easily recognize the increase in motility index. The recording has been performed with a 20-channel manometric catheter (side holes 2.5 cm apart)

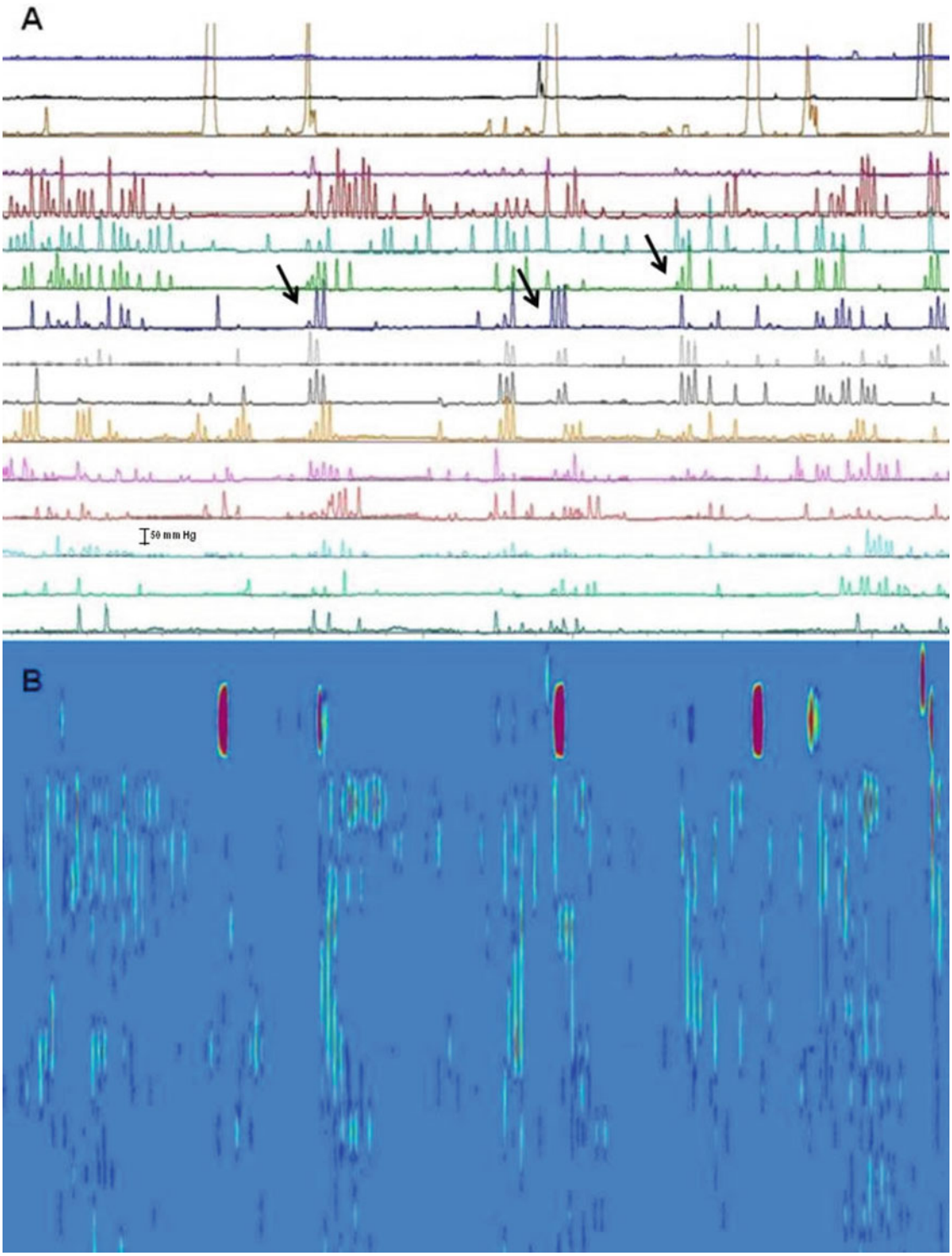

Fig. 8.3 Examples of conventional (**a**) and spatiotemporal plot (**b**) of short burst of contractions (*arrow*) recorded in the duodenum during phase II lasting more than 2 min. They can be clearly distinguished from background pressure wave activity during phase II. The 3rd channel is localized in the antrum. The recording has been performed with a 20-channel manometric catheter (side holes 2.5 cm apart)

over 35 weeks post-conceptional age that a disruption of cyclical activity can be seen with feeds [10].

The presence of other distinct motility patterns has been identified in both healthy individual and patients. *Discrete clustered contractions (DCCs)* or *cluster of contractions (CCs)* are defined as the presence of 3–10 pressure waves of slow frequency, each having a significantly higher amplitude and duration compared to isolated individual contractions [15, 28]. They propagate aborally for less than 30 cm at rate of 1–2 cm s^{-1} and usually show a rhythmic pattern with regular

intervals of quiescence lasting at least 30 s (Fig. 8.3) [3]. DCC are usually recorded during phase II, although they are occasionally seen during the postprandial period (phase III-like activity) [3, 14, 28, 29]. Postprandially, clusters of contractions seem to occur in association with mechanical obstruction or intestinal pseudo-obstruction, and they are characteristically nonpropagated [30]. *Bursts of contractions* are defined as sequences of intense irregular pressure waves, which do not correspond to the definition for phase III or for DCC. They can be clearly distinguished from background pressure wave activity during both phase II and the postprandial period. Short bursts of propagating contractions have been described in healthy individuals, whereas sustained bursts of contractions confined to one limited segment (nonpropagated) lasting for a period of >30 min and associated with tonic intermittent baseline pressure elevation are considered an abnormal neuropathic pattern [21, 31, 32]. *Giant migrating contractions* or *prolonged intestinal contractions* are pressure waves of prolonged duration (>20 s) and high amplitude more than 30 mmHg. In healthy individuals, they occur primarily in the distal ileum and propagate uninterruptedly and rapidly with highly propulsive force over long distance in aboral direction in the small intestine and colon [33, 34].

Technical Aspects

Manometry is by nature a highly technical evaluation. When knowledgeably used, manometric examination provides an accurate description of intestinal neuromuscular function, but only if physical principles and equipment characteristics are respected. In general, manometric data are reliable only if the methodology used to acquire them is accurate.

A manometric apparatus setup consists of a pressure sensor and transducer combination that detects the gastric and small intestine pressure complex and transduces it into an electrical signal and a recording device to amplify, record, and store that electrical signal. The pressure sensor/transducer components of a manometric assembly function as a matched pair and are available in two general designs: either water-perfused catheters connected to a pneumohydraulic perfusion pump and to volume displacement transducers or strain gauge transducers with solid-state circuitry [35].

Low-Compliance Perfused Manometric System

The water infusion system includes a catheter composed of small capillary tubes, a low-compliance hydraulic capillary infusion pump, and external transducers. In adults, the small capillary tubes usually have an internal diameter of approximately 0.4–0.8 mm and an opening or port at a known point along the length of the catheter. In adults, the most commonly used catheters have an overall diameter of 4.5 mm [35]. In children, in order to reduce the diameter of the catheter, smaller capillary tubes (with internal diameters of 0.35 mm) are utilized; moreover the study is performed at lower infusion rates [36]. The manometric probes are usually tailored to the child's size, and the distance between the recording ports should be decided based on the purpose of the investigation [35]. Since one antral recording site is insufficient to provide an accurate recording of antral motor activity due to its continuous forward and backward movement, the manometric catheter should have at least five recording ports with the two most proximal side holes spaced 0.5–1.5 cm apart positioned 1 cm proximal to the pylorus to provide measurements of antral activity, while the remaining side holes are positioned in the small intestine and spaced 2.5–5 cm apart in infants and toddlers and 5–10 cm apart in children and adolescents [35, 36]. Each capillary tube is connected to an external transducer. The infusion pump, a simple and essential device for stationary manometry, perfuses the capillary tubes, providing a constant flow rate without increasing the compliance of the manometric system. When a catheter port is occluded (e.g., by a muscular contraction), there is a pressure rise in the water-filled tubes that is transmitted to the external transducers. High-fidelity recordings of intraluminal pressure are achieved by infusion rates from 0.1 to 0.4 mL min^{-1}, even if they may provide an unacceptable amount of water to small babies or premature infants. In order to overcome this problem, perfusion rates as low as 0.02 mL min^{-1} have been successfully used [37]. Furthermore, for prolonged studies, the use of a balanced saline solution should be considered.

A device activating the pressure transducers, storing their signals, and displaying the latter in such a way to allow immediate interpretation and analysis is needed. The personal computer has become the heart of any manometry system. It interfaces with purpose-designed electronic modules that activate and receive signals from pressure transducers, while commercially available software programs are essential for acquiring, displaying, and storing pressure recording data. Actually, the technical adequacy of different commercially available device recording systems is quite comparable. Probably the dominant consideration that should determine the choice of a system is the level of technical assistance and the training available locally to support the user.

The required characteristics of the manometric recording apparatus are defined by the magnitude of the pressure to be recorded and the frequency content and waveform of foregut contractile waves. It has been shown that the frequency response of manometric systems required to reproduce foregut pressure waves with 98% accuracy is of 0–4 Hz (maximal recordable dP/dt: 300 mmHg/s). Most of commercially available manometric systems can provide a pressure rise rate of 300–400 mmHg/s, which is adequate for faithful recordings in the gastric antrum and small intestine.

Solid-State Manometric System

The main alternative to the water-perfused manometric system is a manometric assembly incorporating strain gauge sensors and solid-state electronic elements [38]. In this system, the manometric probe contains miniature strain gauge pressure transducers built into the catheter at a fixed location along its length, so that pressure changes directly influence the transducers to generate electrical output signals. The probe can be plugged into a small box containing the electronics, which is then connected to the recording device and to a personal computer. In the ambulatory system, the recording devices are blind and need to be connected to a personal computer with the appropriate software to display and analyze the recording. The main advantage of using solid-state catheters is that the pressures are recorded directly from the area and are unrelated to the relative position of the subject; therefore, manometric studies may also be performed with the subjects in the upright position. This, and the fact that it does not require water perfusion, makes solid-state catheters suitable for long-term ambulatory monitoring of the intraluminal pressure [39]. It has been calculated that for a given number of pressure recording points on a recording assembly, solid-state catheters are 20 times more expensive than a perfused manometric assembly. In the last years, the improvement in miniaturizing transducers has allowed the production of solid-state catheter with up to 36 recording channels with an external diameter comparable to that of the water-perfused manometric catheter used in small infants and children. However, there is still a very little experience in pediatric patients.

High-Resolution Manometry

Manometric techniques have improved in a stepwise fashion from few pressure recording channels to the development of high-resolution manometry (HRM), which is a relatively recent technique that enables more detailed definition, both in terms of space and time, of pressure profiles along segments of the gut [40]. This has been achieved by a combination of new manometric assemblies, allowing intraluminal pressure to be recorded from up to 72 pressure sensors spaced less than 2 cm. At the same time, advances in computer processing allow pressure data to be presented in real time as a compact, visually intuitive "spatiotemporal plot" of gastric and small intestine pressure activity. HRM recordings may reveal the complex functional anatomy of the foregut, and recent studies suggest that spatiotemporal plots may provide objective measurements of the intraluminal pressure profile in the small intestine and improve the sensitivity and specificity of manometric recording by removing much of the ambiguity usually encountered using line plot analysis [41]. However, further efforts to define the role of HRM in the diagnosis and management of neuromuscular disorders are needed.

Methodological Aspects

Preparation of the Patient

Before starting the ADM manometric recording, it is important to assess patient information with regard to medical history, symptoms, medication, and allergies. Any drug with a known effect on gastrointestinal motility should be discontinued at least 72 h before the study.

It is important to emphasize that ADM manometry in children is performed in a different fashion to that in adults due to differences in size, cooperation, and neurological and developmental maturation. Performing manometric studies in children require great patience from the operator. The parents should be present during the testing in order to settle the child and to provide the child with a model of cooperative behavior with the physician. The cooperation can also be improved by the use of age-appropriate relaxation techniques. For example, infants may relax with swaddling and the use of a pacifier. Having a favorite toy can comfort toddlers. School age and older children benefit when equipment is shown and explained prior to the procedure. ADM manometry is best performed without sedation [36]. However, in many children, sedation is necessary, and midazolam has been shown to be effective with no or minimal influence on pressure measurement [42]. It is advisable to wait for complete child recovery from any drug effect before starting the motility tests. Finally, before starting the procedure, it is important to obtain and verify a signed informed consent, and it is also necessary to check that the fasting period has been of adequate duration. In healthy children, an overnight fast is enough, whereas in infants at least 4 h are necessary to eliminate nausea, vomiting, and aspiration. In children on parenteral nutrition, it should be stopped 12 h prior to the study, because of the effect of nutrients on hormones, which may affect the intestinal motility [17]. Similarly, blood glucose levels should be carefully assessed, since hyperglycemia inhibits gastric emptying and reduces the occurrence of phase III [43, 44].

Study Procedure

The manometric catheter can be placed either nasally or orally, but there is broad consensus that studies are better tolerated when the catheter is introduced through the nose. The catheter can also be placed through an existing gastrostomy or jejunostomy. The manometric probe should be

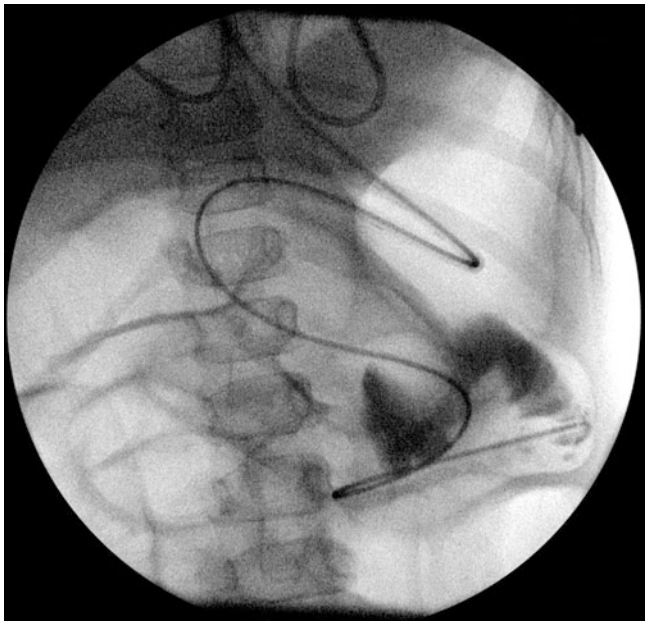

Fig. 8.4 Fluoroscopic placement of ADM catheter. Note the position of the tip is in the distal duodenum at level of the ligament of Treitz

positioned deep enough in the small intestine in order to prevent its falling back into the stomach as a consequence of postprandial gastric distension or duodenal contraction (Fig. 8.4). The tube placement can be performed either fluoroscopically or endoscopically [45]. Under fluoroscopy, the probe placement usually requires high skill to pass the pyloric region, which may be easier with a firm probe rather than a soft, flexible one. The former, however, is more difficult to advance beyond the duodenal bulb due to its acute angle. Moreover, a hard probe may cause greater discomfort during the recording time especially in young children. The addition of a weighted probe tip may facilitate the placement as it utilizes the advantage of gravity. The probe can be also advanced through the pylorus using an endoscope and biopsy forceps, taking care to use as little air as possible to insufflate the bowel, given that overinflation may affect gastrointestinal motility and provoke a backward movement of the manometric probe. In some centers, the manometric recording is performed the day after the tube placement with additional radiology confirmation to ascertain appropriate catheter position, allowing for correction if necessary.

During the manometric recording using a water-perfused system, the patients usually maintain the same position (supine), whereas when using portable solid-state equipment, the patients are encouraged to perform daily activities when possible [35]. Ambulatory manometry is usually performed for 24 h, whereas for stationary manometry, recording must be carried out until a phase III and/or clear-cut abnormalities are recorded. However, it is generally advisable to perform a fasting recording for at least 6 h (or two MMCs) and postprandial recording for at least 90 min [36]. The type and the size of meal should be adjusted according to patient's age and preference. In older children, the test meal should be of at least 400 kcal, in order to ensure an adequate postprandial response in the small intestine lasting for at least 90–120 min [25, 36]. In younger children, the test meal should provide at least 10 kcal kg^{-1}. The meal should be balanced with at least 30 % of calories provided as fat content. However, in some cases, it is impossible to provide a predetermined volume to a patient, e.g., one with severe gastrointestinal dysmotility and inability to tolerate oral or enteral feeding. Finally, if no phase III is recorded during fasting, a drug stimulation test should be performed using iv erythromycin (1 mg kg^{-1} over a period of 30 min), which is able to induce a gastric phase III and allows assessment of its migration in the small intestine [46, 47]. Other agents such as azithromycin, octreotide, amoxicillin/clavulanate, ghrelin, and neostigmine were also found to induce phase III activity; however, there is still a lack of adequate clinical experience in the use of these agents to allow for a general recommendation [48–53].

Analysis of Manometric Recording

Both qualitative and quantitative analysis of the ADM tracings should be performed. Qualitative analysis includes the recognition of specific motor patterns as well as the overall characteristics of the fasting period (typical cyclical pattern of the MMC, characteristics of phase III activity including the total number of phase III occurrences, migration pattern, mean amplitude, mean peak velocity, and intervals) and fed period (presence of change in motility after test meal). Quantitative analysis includes the calculation of distal antral and duodenal motility indices (MI), expressing the contractile activity as the natural logarithm of the area under the manometric pressure peaks above a threshold pressure. Computerized data evaluation, including wave identification algorithms, artifact removal, and algorithms for detection of propagated activity, offers an improved degree of objectivity in the analysis of pressure tracing and can facilitate the quantitative analysis of relevant parameters [54].

A normal motility pattern is defined as the presence of at least one MMC per 24 h of recording (it has been shown that almost 95 % of normal children have phase III within 4-h fasting study), conversion to the fed pattern without return of MMC for at least 2 h after a 400-kcal meal, distal postprandial contractility (MI per 2 h > 13.67), small intestinal contraction >20 mmHg, and absence of abnormal findings described in Table 8.1 [55]. Therefore, the presence and characteristics of the MMC and its response to nutrients are used as a marker of enteric neuromuscular function.

Based on the findings of abnormal manometric features, various clinical/pathophysiological categories of abnormalities

Table 8.1 Manometric features associated with gastrointestinal motility disorders

Interdigestive or fasting period
• Absence of phase III
• Short intervals between phase III
• Abnormal phase III
– Stationary
– Retrograde
• Non-migrating burst of contraction
• Sustained simultaneous cluster of contractions
• Low-amplitude contraction
Postprandial or fed period
• Failure to switch to postprandial period
• Postprandial hypomotility
– Low frequency of contraction
– Low-amplitude contraction
• Non-migrating cluster of contraction

can be recognized [35, 55]. In patients with *enteric neuropathy*, the motor activity is typically disorganized and/or uncoordinated. The most compelling finding is represented by the absence of an MMC during a sufficient recording time (ideally 24 h); however, this scenario is a rare event in patients with enteric neuropathy. More common findings include the presence of retrograde or uncoordinated phase III activity (Fig. 8.5), increased frequency of phase III (in adults and older children >1 MMC cycle per hour) (Fig. 8.6), presence of nonpropagated bursts and sustained uncoordinated phasic activity, antral hypomotility, inability to establish a fed pattern after a test meal, and presence of phase III-like activity in the fed period. In patients with *enteric myopathy*, the normal manometric patterns are usually preserved, but the amplitude of contractions in both preprandial and postprandial periods does not exceed 20 mmHg (Fig. 8.7); however, low-amplitude contractions may also represent a consequence of gut dilatation proximal to an obstructive segment. For this reason, the absence of dilated loops is a prerequisite for a diagnosis of enteric myopathy. In patients with *mechanical obstruction*, multiple simultaneous giant contractions as well as the presence of simultaneous DCCs in the postprandial period are frequently reported. In neonates, the presence of high-amplitude retropropagated contractions should raise the suspicion of mechanical obstruction. In children with *CNS abnormalities*, an abnormal frequency and propagation of phase III, increased proportion of nonpropagated DCCs, antral hypomotility, abnormal proportion between periods of phase I and II activity, and altered postprandial pattern duration with the presence of phase III-like activity have been shown [56]. Finally, in adult patients with *postvagotomy syndrome*, the most common manometric findings are an increased frequency of MMC, the absence of antral phase III and the presence of antral hypomotility after test meal, and altered postprandial pattern duration with a rapid return of MMC activity. An example of the different parameters that should be included in a manometric report is shown in Table 8.2.

Reference Values

Prior to interpreting the recorded data and deciding whether abnormalities of gastric and small intestinal motor activity are present, it is of pivotal importance to define the spectrum of normality. Unfortunately, the lack of normal controls is an important limiting factor for the establishment of normal motility patterns, making the interpretation of manometric recording data difficult and subjective and occasionally leading to overinterpretation. However, some normal values have been published (Table 8.3). Although each center performing ADM should have an own set of normal values, it is suggested that "normal" ranges proposed by one group could be used by another if the investigation is performed and interpreted in the same way.

Indications

Although ADM is indicated in patients with otherwise undiagnosed gut motility disorders unresponsive to conventional therapies and whose quality of life is substantially impaired (by symptom severity and the diagnostic uncertainty), it is a rather cumbersome procedure to perform, not always easy to interpret, and practically useful in the clinical management of only a minority of patients. For instance, it has been shown in children that there is an excellent interobserver agreement for the number of fasting phase III and their measurement, whereas the interobserver agreement for the detection of other motor abnormalities, such as sustained phasic contraction and postprandial simultaneous clusters, is significantly low [57]. Therefore, given that the small bowel manometry requires expertise and dedicated equipment and personnel, it should be ideally performed in a limited number of referral centers with a specific interest in the field.

ADM serves to clarify a clinical diagnosis of abnormal motility or exclude a gastrointestinal (GI) motility disorder. There are only a few indications for the test (Table 8.4). Manometry is indicated in children with suspected chronic intestinal pseudo-obstruction in order to verify the diagnosis, clarify the pathogenesis, and optimize clinical management [58]. For instance, the presence of a myopathic pattern is an indicator of a poor response to enteral feeding, whereas the presence of MMC predicts clinical response to prokinetics therapy and success of enteral feeding [59, 60]. Manometric assessment may allow determination of the extent of disease (localized or diffuse) and the optimal route for nutritional support (gastric, enteric, or parenteral). ADM may be useful in

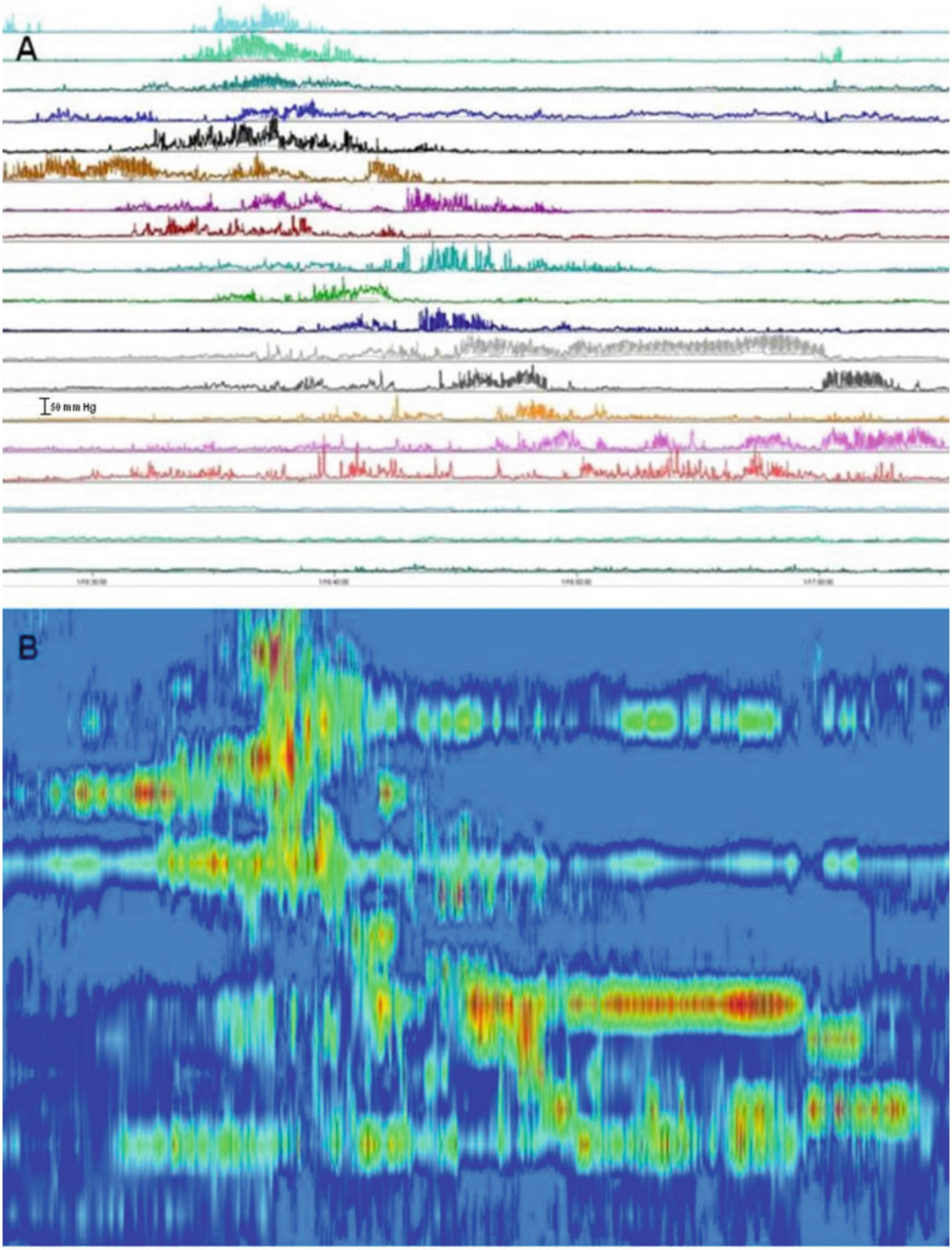

Fig. 8.5 Examples of conventional (**a**) and spatiotemporal plot (**b**) of an abnormal propagation of phase III in a child with neuropathic pediatric chronic intestinal pseudo-obstruction (PIPO). The 5th channel is localized in the antrum. The recording has been performed with a 20-channel manometric catheter (side holes 2.5 cm apart)

guiding the intestinal transplantation strategy in children with chronic intestinal pseudo-obstruction by identifying the extent of GI dysmotility [60]. Severe gastric or duodenal motor abnormalities seem to compromise the postoperative course of the intestinal graft recipient. In patients with intractable constipation, ADM manometry should be performed if surgery is

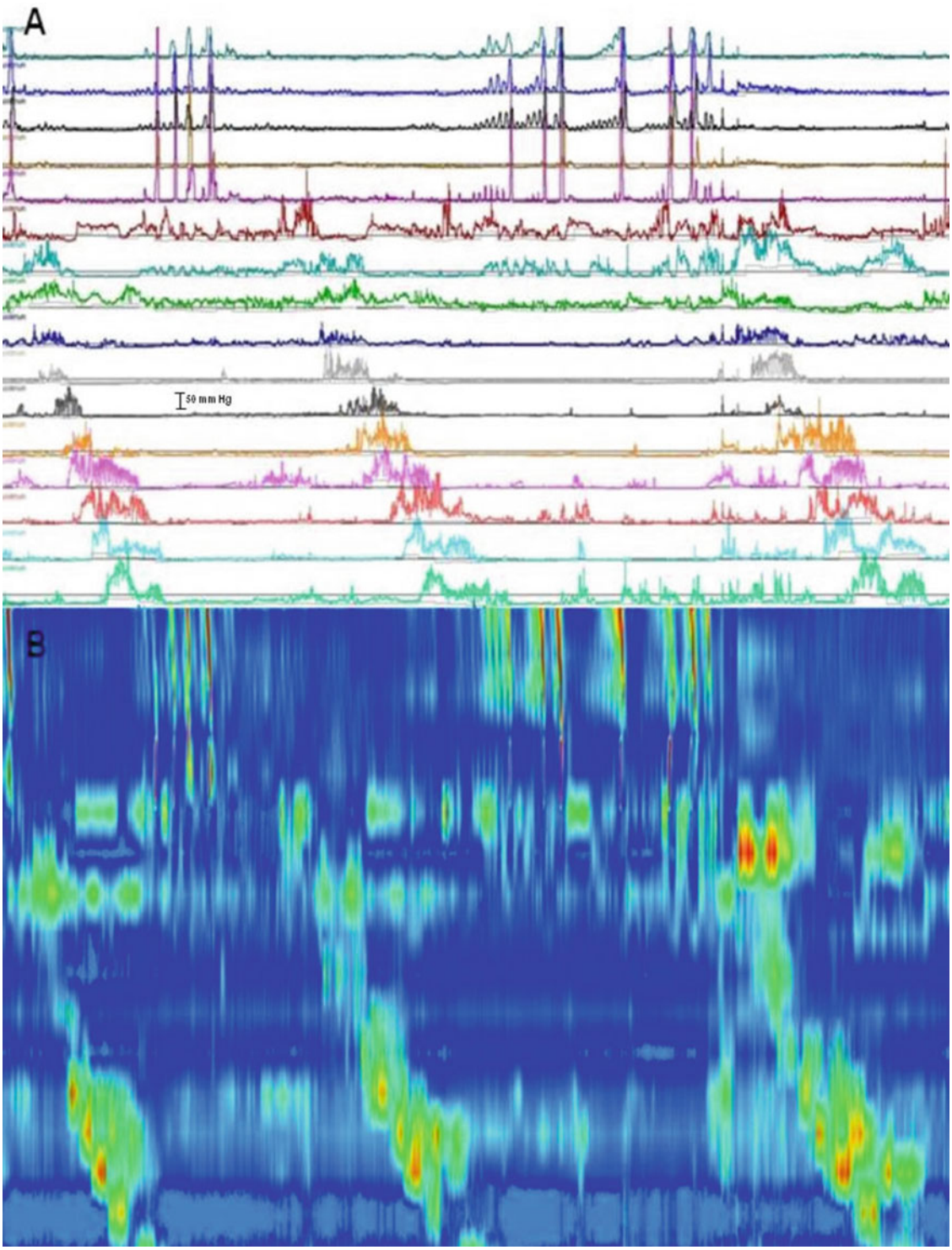

Fig. 8.6 Examples of conventional (**a**) and spatiotemporal plot (**b**) of short intervals of phase III in a child with neuropathic chronic intestinal pseudo-obstruction (PIPO). Phase III occurred separated by interval of 10–15 min. Note also the tonic component within phase III, which is defined as an elevation of the baseline more than 10 mmHg for longer than 1 min. The recording has been performed with a 20-channel manometric catheter (side holes 2.5 cm apart)

being considered, given that patients with small bowel dysmotility have generally a poor outcome after the surgery. ADM is also indicated in patients with recurrent subocclusive episodes, in order to differentiate a pseudo-obstructive syndrome from a mechanical obstruction, which may sometimes be overlooked even by an experienced radiologist [61].

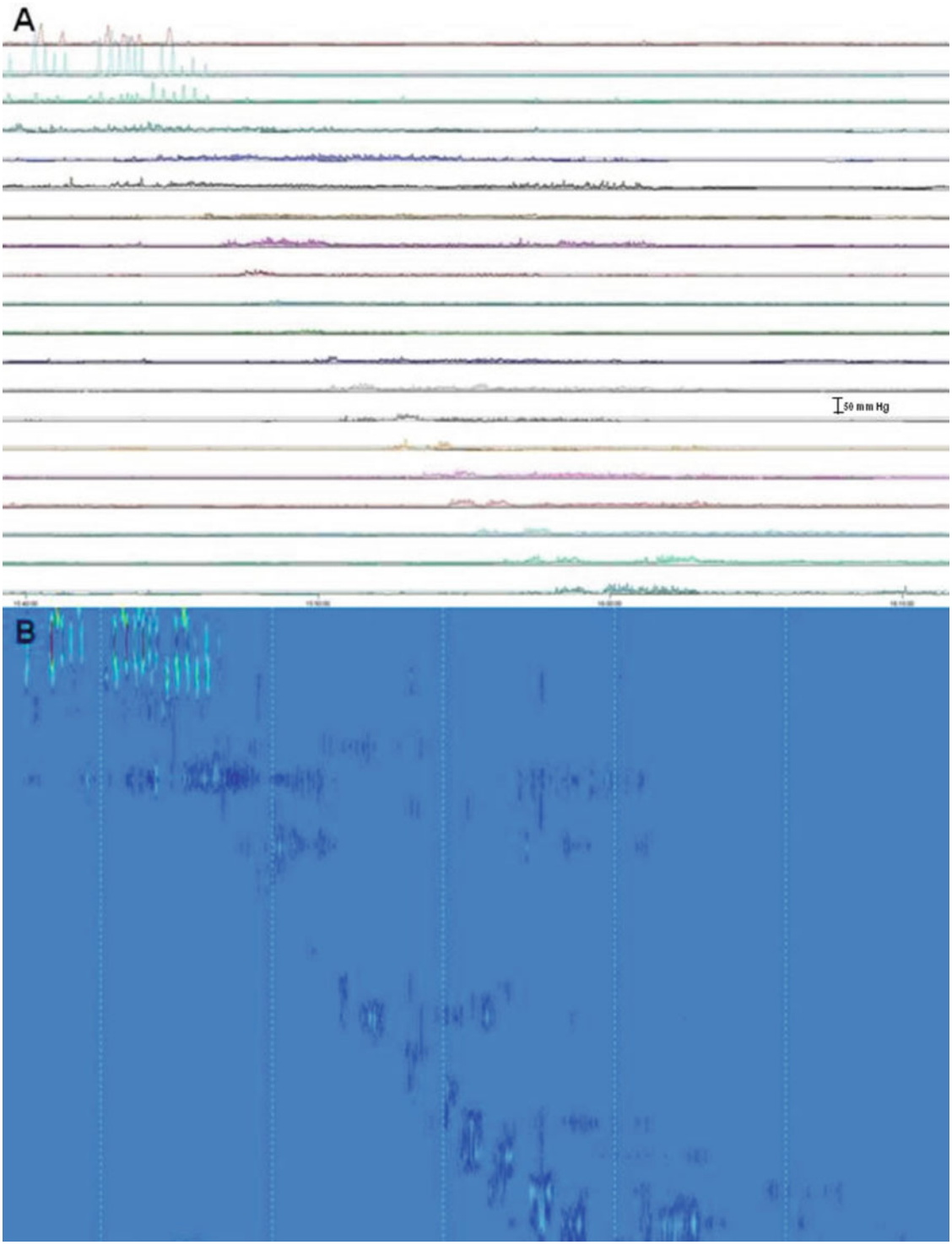

Fig. 8.7 Manometric tracing in a child with myopathic pediatric chronic intestinal pseudo-obstruction (PIPO). Note the low amplitude but normal propagation of phase III and the paucity of other contractile activities in the small intestine in both conventional (**a**) and spatiotemporal plot (**b**). The recording has been performed with a 20-channel manometric catheter (side holes 2.5 cm apart)

Manometry is indicated in the investigation of children with severe unexplained gastrointestinal symptoms, such as vomiting, nausea, abdominal distension, and abdominal pain who fail to respond to an appropriate therapy, and in this context, the test helps to differentiate between vomiting and rumination [62, 63]. For instance, in children with suspected rumination syndrome, the ADM is useful in confirming the diagnosis by showing a characteristic motor pattern, characterized by

Table 8.2 Components of the report

General information
1. Patient ID
2. Date and time of the procedure
3. Referring physician
4. Medication used during the test
5. Person performing the study
6. Type of catheter used
7. Indications for the study
8. Study duration
9. Test meal (y/n); route of delivery; calories eaten
10. Catheter placement (nostrils/gastrostomy)
11. Position of the catheter tip (?beyond DJ flexure)
12. Any significant symptoms reported
Fasting period: analysis of 3 distinct phases of MMC (presence, propagation, and duration)
1. *Number and duration of cycles of all 3 phases*
2. *Phase III*
– Highest contraction frequency of the duodenum
– Highest contraction frequency of the duodenum
– Highest contraction frequency of antral activity (normal 3 cpm)
– Highest amplitude (normal > 20 mmHg)
– Presence of phase III
– Duration of phase III (normal 3–4 min)
– Number of phase III during the study
– Propagation of phase III (normal/abnormal)
3. *Phase I*
– Duration (normal 40–50 min)
4. *Phase II*
– Frequency
– Presence of discrete clusters of contractions
– Presence of single bursts of contractions (single, propagated, simultaneous)
5. *Presence of symptoms*
6. *Drug stimulation*
Postprandial
1. Start and end of the meal should be stated
2. Presence of postprandial contraction pattern (fed response)
3. Duration of postprandial phase (normal at least 2 h after meal ingestion)
4. Pre- and postprandial motility index (MI) calculated 30 min before and 30 min after test meal
5. MI ratio (ratio between postprandial and preprandial motility index)
6. Amplitude ratio (ratio between postprandial and preprandial amplitude)
Interpretation

postprandial simultaneous pressure increases at all recording sites [62]. This is covered elsewhere in the book. Finally, an entirely normal study in children clinically suspected of having a severe dysmotility syndrome may help to redirect the diagnostic effort and may result in the consideration of other diagnoses such as fabricated or induced illness (formerly Munchausen's by proxy syndrome) [64, 65].

Table 8.3 Normal values for preprandial motor activity (mean and ranges) [8, 9, 12, 23]

Parameter	Infants	Children	Adolescents
Duration of phase I—small intestine (min)		12	
Duration of phase II—small intestine (min)		40	
Duration of phase III (min)			
• Antrum	3.5 (3, 4)		
• Small intestine	3.5 (3–7)	4.4	5.0
Amplitude of phase III contractions (mmHg)			
• Antrum		131.8	
• Small intestine	20 (15–30)	55.3	35 (30–40)
Frequency of phase III contractions (contr./min)			
• Antrum	3.3 (3–3.5)		3 (2.5–3.5)
• Duodenum	12 (11–12.5)		11.3 (10.8–11.6)
Migration velocity of phase III (cm/min)			
• Stomach to duodenum	2 (1–4)		12 (7–30)
• Duodenum/jejunum	2.5 (1–5)		9 (3–15)
Interval of phase III (min)		103.9	100 (40–240)

Adapted from Tomomasa T. Antroduodenal manometry p 195–214. In Pediatric Gastrointestinal Motility Disorders. Hyman PE ed. Academy Professional Information Service

Table 8.4 Clinical indications for antroduodenal manometry

1. Clarify the diagnosis in patients with unexplained nausea, vomiting, or symptoms suggestive of upper gastrointestinal dysmotility
2. Differentiate between neuropathic vs. myopathic gastric or small bowel dysfunction in patients with chronic intestinal pseudo-obstruction
3. Identify generalized dysmotility in patients with colonic dysmotility (e.g., chronic constipation), particularly prior to subtotal colectomy
4. Confirm diagnosis in suspected chronic intestinal pseudo-obstruction syndromes when the diagnosis is unclear on clinical or radiological grounds
5. Assess for possible mechanical obstruction when clinical features suggest, but radiological studies do not reveal, obstruction
6. Determine which organs need to be transplanted (isolated vs. multi-visceral transplantation) in patients with chronic intestinal pseudo-obstruction being considered for intestinal transplantation
7. Confirm a diagnosis of rumination syndrome

Conclusion

Antroduodenal manometry provides relevant physiological information on the neuromuscular activity of the foregut and is useful in diagnosing and guiding the management of enteric neuromuscular disorders. Because of the complexity in performing and analyzing ADM, it requires considerable experience and skills that may only be available in referral

centers with a specific interest in the field of GI motility. The development of recording equipment and advanced computer analyses that are in progress appear to have the potential to substantially improve our understanding of normal and abnormal foregut neuromuscular function.

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Colonic Manometry

9

Desale Yacob and Carlo Di Lorenzo

The colon is tasked with what appears to be a mundane and unsophisticated function of stool disposal. This task is however very complex and is accomplished by a number of unique and diverse motor activities all working in synchrony. The colon's main functions are achieved through slow net distal propulsion, continuous mixing, exposure to mucosal surfaces, and tonic and phasic intraluminal pressure changes. The organized patterns that make this process efficient have specific characteristics at different regions of the colon. Much is known about the in vitro activity on a cellular level of this process; however, there are still unanswered questions regarding the in vivo activity, in part due to the lack of a suitable animal model. The introduction of colonic manometry and recent innovations in both its technique and the modalities of catheter placement have now made it possible to understand more thoroughly the motor characteristics of the entire colon.

Normal Physiology of Colonic Motility

The process of defecation has two stages, the first being an involuntary phase during which fecal content is transported to the rectum, followed by a second phase that is both voluntary and involuntary. During the latter phase, intra-abdominal pressure increases along with descent of the pelvic floor and straightening of the anorectal angle. The increase in rectal pressure results in an involuntary relaxation of the internal anal sphincter, followed by expulsion of stool when the external anal sphincter relaxes [1]. Normal colorectal motility involves the coordinated activity of the enteric muscles, the enteric nervous system (ENS), and the interstitial cells of Cajal (ICC) and is modulated by the sympathetic and parasympathetic components of the autonomic nervous system. The ENS provides the gastrointestinal tract a local nervous mechanism within its walls. However, although the various intestinal functions are regulated locally by the ENS, its control of intestinal motility is modified and enhanced by inputs from the central nervous system and other entities that reside in the gut. The myenteric plexus controls the motor function by directly innervating the circular and the longitudinal muscle layers of the colon. Sensory input affecting motility is accomplished via intrinsic sensory neurons which are activated by stretch and muscle tension. They are also activated by intraluminal chemical stimuli that act on the chemical and mechanical receptors found within the mucosal epithelium [2, 3]. The autonomic nervous system, via the sympathetic nervous systems, directly innervates smooth muscle, but a large amount of its influence is indirectly mediated by influences on the enteric neuronal circuits. The parasympathetic nervous system is influenced primarily by vagal efferents to the proximal colon [4]. There is little or no vagal effect beyond the distal colon where sacral parasympathetic influences come into play. The sacral parasympathetic pathways are identified as being responsible for the process of defecation [5].

How to Perform the Study

The contractile function of the colon in children has traditionally been measured using catheters which are placed within the colonic lumen, with pressure-sensitive ports placed along the catheter length. The catheter types, their placement techniques, and the software for data analysis have all evolved over the past few years, leading to a more sophisticated mapping of the colon's motor function.

Water-perfused catheters have been in use for many years and are still being employed by many centers. It is important to note that most published pediatric studies utilized

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water-perfused catheters, and hence the basis for most of our understanding of the subject matter emanates from this methodology. The spacing between the recording sites of these catheters is variable but usually ranges between 5 and 15 cm, based upon the age of the child and the length of the colon to be studied. Each port is connected via a separate lumen (channel) to individual strain gauge pressure transducers, allowing multichannel studies. Perfusion is at a constant flow rate and is achieved by use of distilled water at constant pressure [6]. Contractions of the colonic wall occlude the manometric opening and impede the flow of water. Resistance to flow is measured as pressure change. The advantages of this system include its simplicity, the relatively inexpensive components, and the ease of sterilization. These catheters are also available in disposable versions. There are both technical and nontechnical disadvantages to this system. The technical disadvantages include the need for the patient to be connected to a stationary apparatus, the amount of water infused during prolonged studies which can potentially place small infants at risk for water intoxication, and the large spacing between the pressure sensors, making it hard to detect contractions that propagate for short distances.

More recently, high-resolution catheters are being utilized more often to perform colonic motility testing. These solid-state or fiber-optic catheters contain multiple recording sites that are closely spaced and require more advanced software for analysis. The new technology is proving to be superior in providing a more precise mapping of the colon's complex motor function, thus remedying the deficiencies of the older system. Such catheters can be custom designed to have transducers or fiber optics that are spaced as close as 1 cm apart or however one wants them depending on the specific purpose of the catheter (e.g., research vs. clinical use). Solid-state catheters were found to be as reliable at detecting high-amplitude propagating contractions (HAPCs) when compared to the water-perfused ones [7]. The use of solid-state catheters permits to capture the transmitted signals by a portable digital recorder, thus allowing ambulatory studies and the ability to measure more representative time periods for analysis. Disadvantages include the significantly higher cost and the relative fragility of the equipment.

Catheter Placement

Placement of colonic catheters constitutes one of the most challenging portions of the testing in children. In pediatrics, the placement is done transanally, in a retrograde fashion, except in the presence of ostomies which may allow placement of the catheter through the ostomy in an antegrade or retrograde manner depending on the location of the ostomy. Colonoscopic placement requires bowel preparation which some studies have suggested may affect basal motor activity [8, 9]. Different endoscopic techniques can be used for the placement. A biopsy forceps can be passed through the biopsy channel, grasping the manometry catheter via a suture loop tied to the catheter tip. The catheter is then advanced along with the colonoscope to the desired location, the forceps is opened, and the scope is then slowly retracted suctioning as much air as possible. Recently, it has been the practice of many to have the catheter clipped to the colonic mucosa, making it less likely for it to be dislodged during testing (Figs. 9.1 and 9.2) [10]. This can be accomplished by grabbing the suture loop with a hemostasis clipping device that is then deployed on a mucosal fold when the desired location has been reached and the catheter is released. Once the test is complete, a gentle pull is all that is needed to remove the catheter. In our center, the suture is tied to both the tip of the catheter and to one of the endoclip prongs that has been passed through the biopsy channel of the scope, which is then closed and pulled back into the channel. Successful placement requires skilled maneuvers and patience given the redundant and dilated distal colon that is

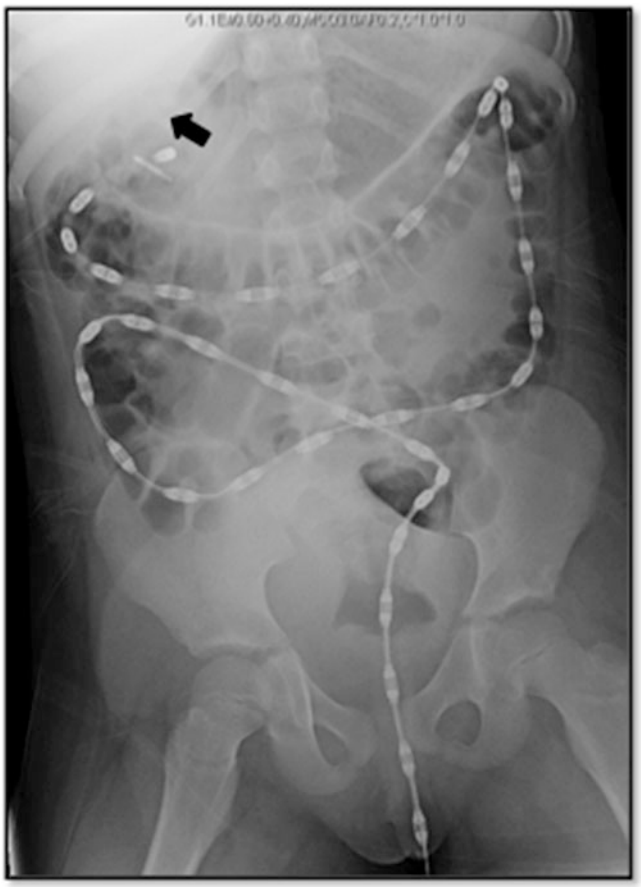

Fig. 9.1 Abdominal radiograph showing a high-resolution solid-state colonic motility catheter placed with its tip at the hepatic flexure. The *arrow* points to the endoclip used to secure the catheter in place

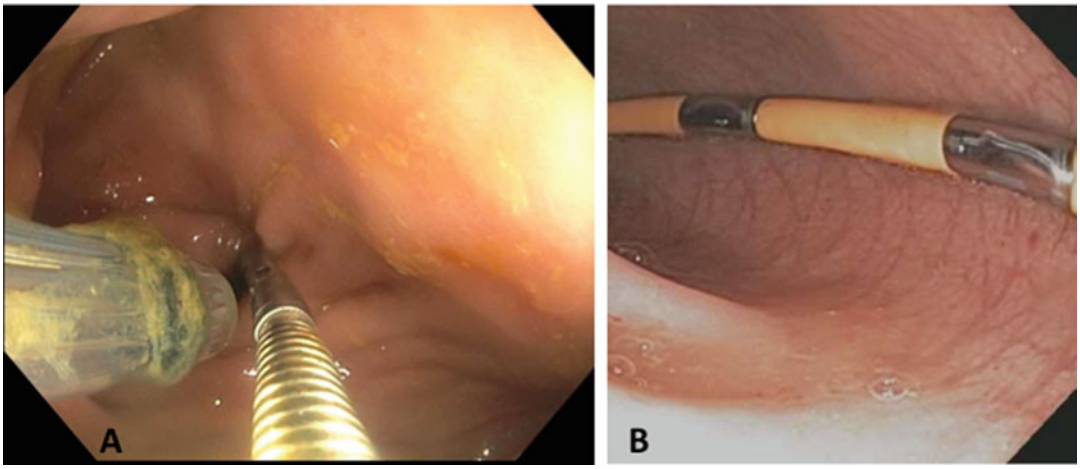

Fig. 9.2 Endoscopic image of colonic motility catheters, (**a**) water-perfused catheter in the process of being clipped to a fold in the cecum and (**b**) a solid-state catheter in the colonic lumen with the pressure sensors in silver

common in the patient population needing manometry evaluation. An alternate transrectal placement technique uses a guidewire passed though the biopsy channel and left in place during the removal of the colonoscope. The manometry catheter is then advanced over this guidewire with fluoroscopic assistance. It should be emphasized that in children the endoscopic placement is always done under deep sedation or general anesthesia. The dilated and redundant colons of patients with severe and chronic constipation are not always easy to cleanse with regular cleanout regimens prior to colonoscopy. Our practice has been to begin the cleanout at home with high-dose polyethylene glycol 3350 and bisacodyl followed by a 1-day admission for an inpatient cleanout prior to the catheter placement and testing. Fluoroscopic placement of the catheter into the proximal colon may also be performed by skilled interventional radiologists, but it is associated with exposure of the patient to radiation [11].

Study Protocol

There is variability in study protocols with no prospective data indicating superiority of any specific one. Studies of relatively short duration, approximately 4–8 h, are usually adequate to evaluate response to stimuli and form a plan of intervention. However, studies lasting 24 h performed in ambulating subjects provide more physiologic data. Provocation tests are used to assess response to stimuli such as food and medications. Food is the most powerful physiologic stimulus of colonic motility, and its ingestion induces an increase in phasic and tonic motor activity, also known as the gastrocolonic response. The early response is most intense in the distal colon and may result in an urge to defecate. A second peak in motility is seen after 50–110 min lasting up to 3 h. Increased motor activity following a meal may be regarded as an indication of the integrity of the neurohumoral control of colonic motility. The postprandial observation period is typically followed by administration of a stimulant laxative directly into the colon. The expected response to such a provocative intervention in individuals with normal motility is the occurrence of HAPC [12, 13]. Absent response has been interpreted as being diagnostic of colonic inertia and myenteric plexus damage in adults and children [14, 15]. Stimulation with other drugs, such as neostigmine, and use of a barostat to measure tonic changes are not routinely done in children.

Pediatric studies are initiated after the effect of the sedation or the anesthesia used for placement of the catheter has resolved. Some have suggested the study can be performed as early as 4 h after recovering from anesthesia [16], but others have recently reported an important effect of anesthesia on the study interpretation when study is performed the same day of anesthesia [17]. The study can be safely performed the same day when colonoscopy is performed with intravenous sedation (benzodiazepines). Typical protocols in pediatrics start with fasting period when baseline colonic motility without stimulation is monitored for 1–2 h. The child is then offered and asked to eat a large, age-appropriate meal. The postprandial motility is recorded for at least one more hour starting at the end of meal. Pharmacologic provocation is then usually performed with 0.2 mg/kg of bisacodyl (max 10 mg), which is infused through the motility catheter into the most proximal portion of the colon or via an ostomy opening if present (Fig. 9.3). Symptoms experienced by the child are noted during the entire study. It is particularly informative to observe the child's reaction to the onset of the urge to defecate associated with the administration of bisacodyl. Thus, it is imperative that a nurse or a physician is in the room with the child undergoing the test at all times. The patient is most likely to report abdominal cramping and

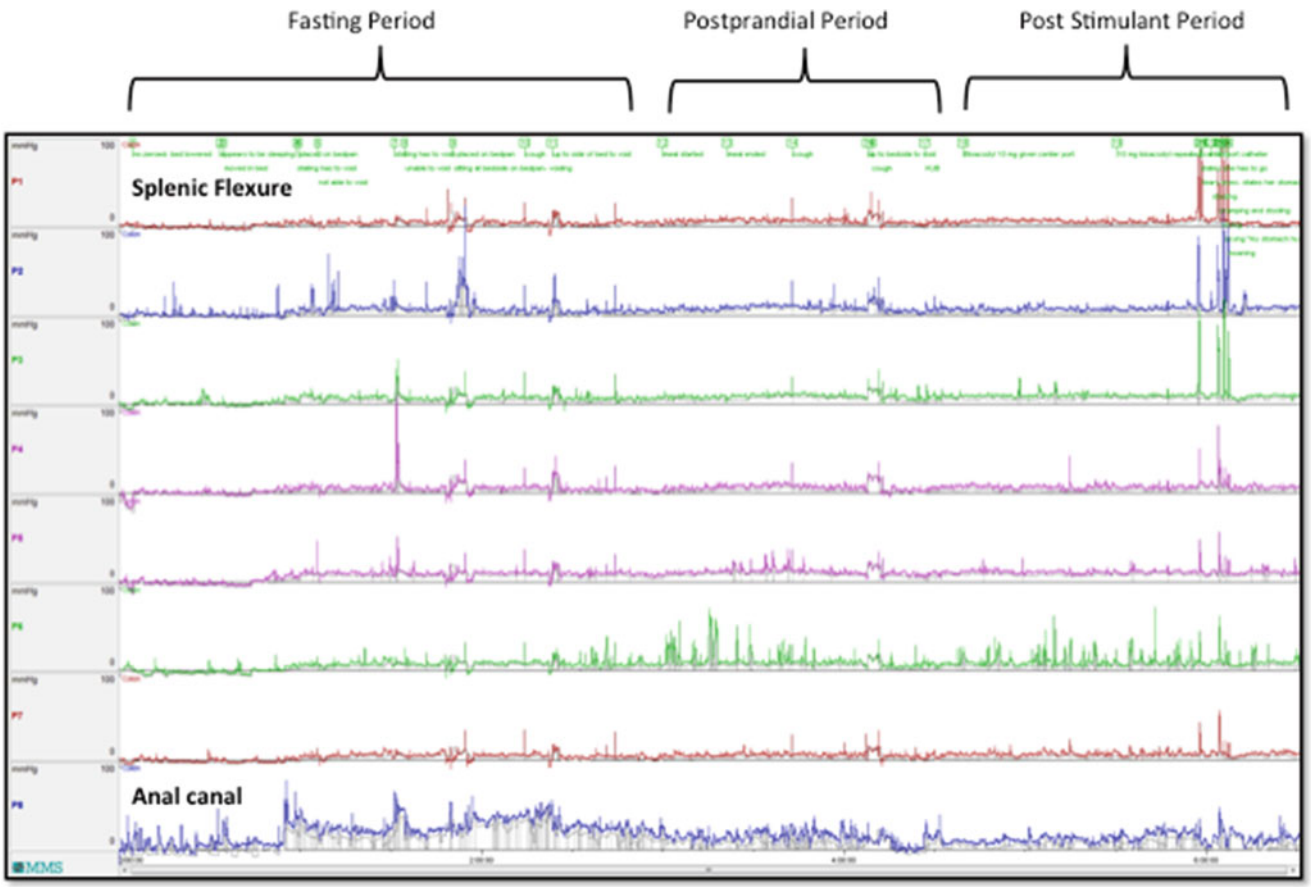

Fig. 9.3 A 6-h-long colonic manometry study with fasting, postprandial, and post-stimulant motility tracing

have a bowel movement as a result of the HAPC. It is not unusual for the child's withholding behavior to be finally recognized as such by the parents once it is pointed out by the medical provider observing the study. Some children wrongly identify the cramping that is due to colonic contractions with pain or deny any sensation and elect to lay in bed instead of heading to the commode. The feedback from the medical provider as this is taking place has the potential to be very educational to both the patient and the parents [18].

Identifiable Motility Patterns

High-amplitude propagating contractions (Fig. 9.4) are defined as contractions with an amplitude of greater than 80 mmHg, a duration of greater than 10 s, and propagation of 30 cm or more. They are expected to stop at the junction between sigmoid colon and rectum. They typically occur following meals, upon awakening, and can be induced by bisacodyl, glycerin, and other colonic irritants. They are more common in younger children [19] and in patients who have had a distal colonic resection, such as in patients after surgery for Hirschsprung's disease [20]. Recent studies have also shown that propagated contractions of varied amplitude can also be induced by saline infusion and distention of the right colon [21, 22]. Low-amplitude propagating contractions (LAPC), in contrast to HAPC, are defined as having amplitude of less than 50 mmHg. They occur 45–120 times per 24 h and are typically 5–40 mmHg in amplitude. They occur significantly more often during the day than at night and, much like HAPC, increase in frequency following meals and upon waking [23, 24]. The function of LAPC is poorly understood. They are likely to be associated with lesser propulsive movement of intraluminal contents and have been reported to be involved with the transport of less viscous colonic contents, such as fluid or gas [25].

An increase in colonic motility, often measured as the "motility index" (a parameter which takes into account both frequency and amplitude of contractions), is expected after ingestion of a meal. The increase in motility involves both tonic and phasic contractions and may be difficult to quantify especially when the postprandial period is associated with motion artifacts. Evaluation of postprandial changes in colonic tone using the electronic barostat is not commonly

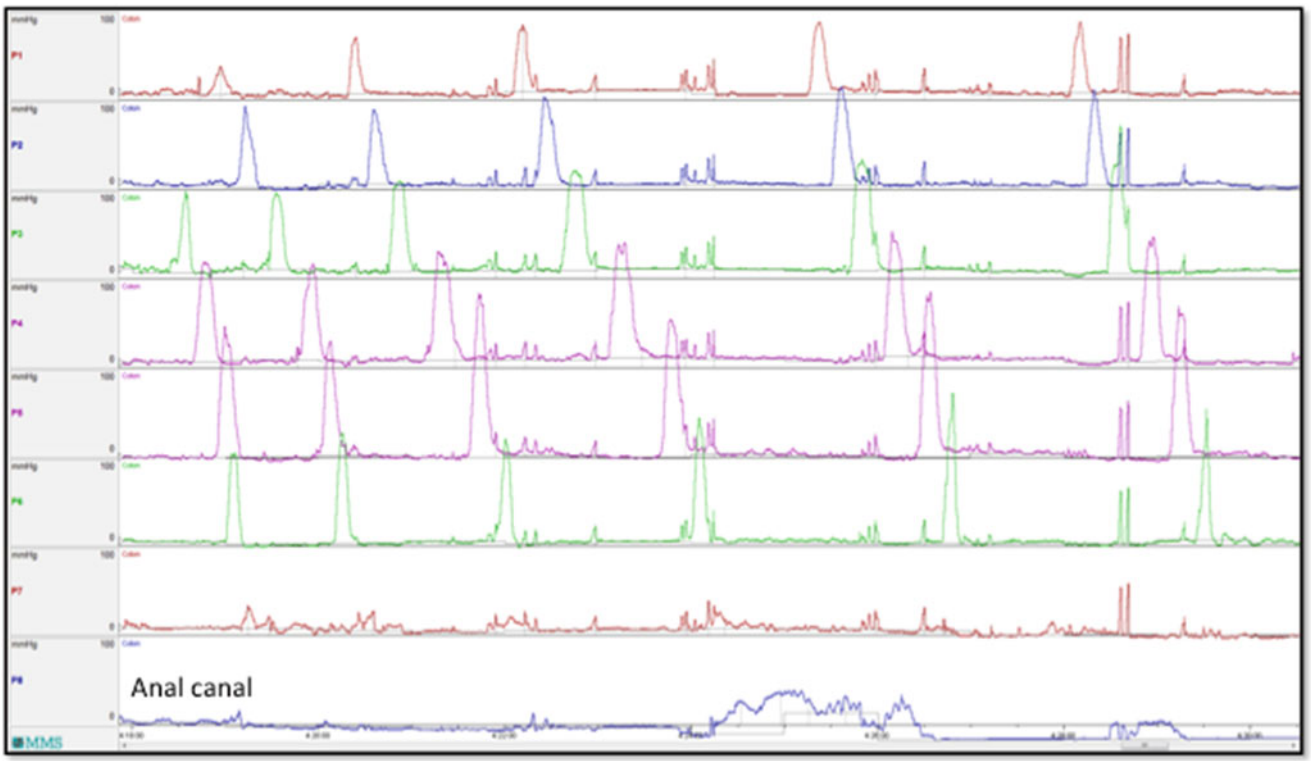

Fig. 9.4 Example of a cluster of high-amplitude propagating contractions (HAPC) recorded with an 8-recording-site water-perfused catheter

done in children [26]. Visual interpretation of the gastrocolonic response produces the maximum variability in interindividual interpretation of the test. On the other hand, there seems to be great concordance among different investigators in the recognition of HAPC. The median agreement regarding the overall interpretation of the colonic manometry in children being either normal or abnormal is 87 % [27].

Indications for the Study

1. Severe constipation
   (a) To assess patients with constipation unresponsive to adequate medical therapy
   (b) To guide surgical interventions including placement of diverting stoma, segmental colonic resection, or formation of a conduit for administration of antegrade enemas
   (c) To evaluate the function of a disconnected colon before possible closure of a diverting ostomy
2. Chronic intestinal pseudo-obstruction
   (a) To determine if the colon is involved in the disease
   (b) To help plan which organs to transplant before a small bowel transplant
3. Hirschsprung's disease and repaired imperforate anus
   (a) To clarify the pathophysiology of persistent symptoms after removal of the aganglionic segment or repair of anorectal malformations when there is no anatomical abnormality likely to explain the symptoms

Constipation

Most children with constipation have functional constipation, a condition related to a maladaptive response to an uncomfortable defecation. A small proportion of children with constipation have symptoms unresponsive to aggressive medical and behavioral therapy which are severe enough to dramatically affect quality of life. In constipated children, especially in the presence of fecal incontinence, the chronicity of the symptoms can be very frustrating and may lead to distrust of the medical team and loss of self-esteem for the child. Colonic manometry is indicated for the evaluation of such children in order to discriminate normal from abnormal colonic motor function [28, 29] which may be associated with an underlying colonic neuromuscular disease (Fig. 9.5). This information can then be used to guide management [30]. Resection of colonic segments found to have abnormal motor function leads to improvement in symptoms [31, 32]. Interestingly, there seems to be little or no correlation between manometric findings and histopathologic abnormalities, suggesting that our current ability to study the morphology and function of the enteric neuromusculature is limited [33].

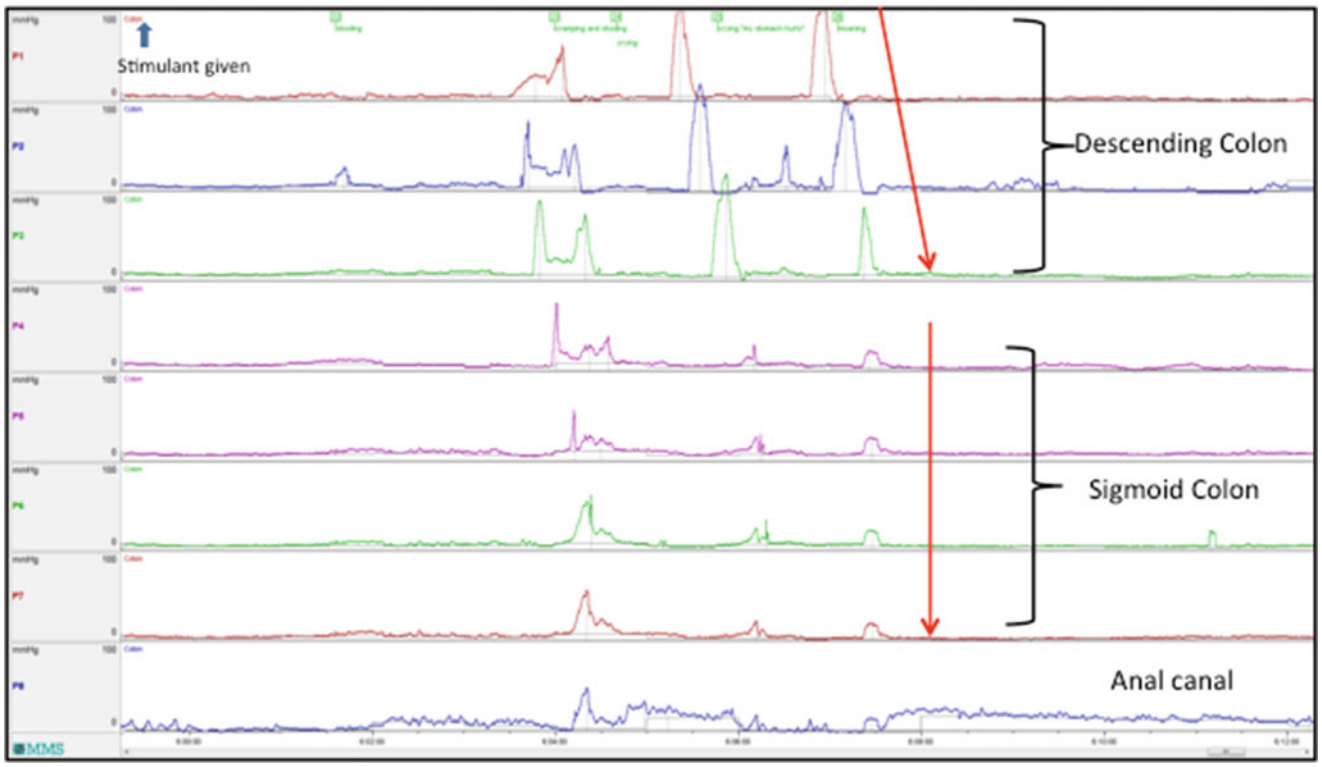

Fig. 9.5 Post-stimulant tracing of normal high-amplitude propagating contractions in the descending colon and abnormal non-propagating low-amplitude pressurization in the sigmoid colon

A study by Villareal et al. used HAPC as a marker for intact neuromuscular colonic function [34]. The colonic manometry pattern, namely, the failure to demonstrate colonic HAPC, directed the providers to the formation of a diverting ostomy (ileostomy or colostomy). In patients who had evidence of a dilated colon with abnormal motility patterns, repeat manometry testing after a period of decompression (5–30 months) led to an improved motor function. Aspirot et al. evaluated the effect of chronic use of antegrade enemas on colonic motility in children and adolescents with severe constipation [35]. All children with abnormal manometry prior to cecostomy placement showed improvement in colonic motility after using antegrade enemas for at least 1 year. Colonic manometry may also be used to predict clinical response to antegrade enemas. Retrospective studies have indicated that patients with HAPC and an intact gastrocolonic response are more likely to have a satisfactory outcome when receiving antegrade enemas [36, 37]. The propagated contractions seem to be essential to propel colonic contents during antegrade irrigation. However, the motor response is still not a guarantee for success, as even some patients with intact HAPC have had a poor outcome, indicating that motility pattern is important, but there are additional factors, such as compliance with the antegrade enema schedule and anorectal and pelvic floor function, possibly playing a role.

Chronic Intestinal Pseudo-obstruction

Chronic intestinal pseudo-obstruction (CIPO) is a heterogeneous group of disorders that vary in cause, severity, course, and response to treatment. Di Lorenzo et al. studied patients with CIPO and found a subgroup of patients with chronic constipation as part of their CIPO symptomatology who had abnormal HAPC, absent gastrocolonic response, or complete lack of identifiable colonic motor activity [38]. A thorough manometric evaluation including colonic manometry needs to be performed during the evaluation for possible isolated small bowel or multivisceral transplantation in children with CIPO, in order to assess which organs need to be transplanted and if a permanent diverting ileostomy will be needed [39].

Hirschsprung's Disease and Anorectal Malformations

After resection of the abnormally innervated bowel in Hirschsprung's disease, a large percentage of patients continue to struggle with abnormal defecatory function [40]. Our approach to these patients, in collaboration with the surgical team, is to first evaluate for anatomical abnormalities, presence of a residual aganglionic zone, absence of dentate

lines due to iatrogenic damage, and quality of anal sphincter function. A contrast enema is used to assess the anatomy and rule out obstructive Soave cuff, bowel stricture, or colonic twist. That is followed by an anorectal manometry, an examination of the anorectal area under general anesthesia, and a repeat full thickness biopsy to assess anal sphincter basal pressure, integrity of the anal canal, and presence and quality of ganglion cells, respectively. If necessary, colonic manometry is then performed for further evaluation. The findings on colonic manometry testing may be classified into four groups, each associated with different physiology [41]. Each category directs different therapy: (1) The first group of patients has HAPC which progress through the neorectum all the way to the anal verge. The amplitude of the HAPC exceeds that of the voluntary contraction of the external anal sphincter. The result is incontinence or rectal pain as the patient attempts to retain the stool. (2) The second group has normal colonic motility with fear of defecation and stool withholding. The negative experience related to attempted defecation before surgical removal of the aganglionic segment or in the postoperative period may result in fecal retention. Identification of normal colonic manometry pattern in these children provides reassurance in the diagnosis and more confidence in the behavioral and medical treatment plan. (3) Abnormal colonic manometry with lack of HAPC, poorly propagating HAPCs, or simultaneous increases in pressure in the distal colon (Fig. 9.5) may be due to a neuropathic motility disorders proximal to the aganglionic segment, possibly associated with intestinal neuronal dysplasia [42] or with a common cavity phenomenon. (4) Finally, a small number of patients with defecation disorders postsurgery for Hirschsprung's disease have normal colonic motility and a hypertensive anal sphincter. Successful treatment options for this subset of patients have included myectomy, which leads to irreversible destruction of the internal anal sphincter and potential risk of incontinence, and botulinum toxin injection into the hypertensive anal sphincter without the risk of permanent sphincter damage but with the need for repeated injections [43–45]. Similar findings have been described in children with continence disorders after anorectal malformations repair. Heikenen et al. have reported that propagation of excessive numbers of HAPCs into the neorectum as well as internal anal sphincter dysfunction can contribute to fecal incontinence in these children [46].

Additional Types of Studies

Ambulatory 24-h Colonic Manometry

A limitation of traditional colonic manometry studies is the duration of the study. There is a well-established circadian variation in colonic motility which is missed during short studies [24, 47–49]. Twenty-four-hour colonic manometry has been proposed as a more informative test which evaluates a time period felt to be more representative of the normal patient's environment and eating and sleeping patterns. It has been performed in children using water-perfused probes [50], but it is best done using solid-state catheters which do not confine the patient to a restricted environment. Solid-state probes have been placed via colonoscopy with clips adhering to multiple sites of the colonic wall. The patient is allowed to ambulate, eat, and defecate in a hospital setting for 24 h with continuous manometric measurement. It is unclear how much the additional information collected during a 24-h study changes clinical management compared to a shorter study with meal ingestion and pharmacological stimulation.

Wireless Motility Capsule

This tool has been approved by the US Food and Drug Administration (FDA) for measurement of gastric emptying and whole gut transit time. Once swallowed, this fairly sizable capsule (diameter and length similar to a video capsule) is capable of measuring intraluminal pH, pressure, and temperature throughout the entire gastrointestinal tract. Data is transmitted to a data receiver and downloads to a computer for analysis. Gastric emptying is measured by timing the point from ingestion to the point where the pH rises above pH6, indicating that the capsule has left the acid environment of the stomach and has entered the more neutral pH of the duodenum [51]. Because it has a single pressure measurement, propagation of motor activity cannot be defined. Wireless pH motility capsule has been found to be useful in evaluating colonic transit and has been validated in adults as an alternative to radiopaque markers as a tool to assess colonic transit [52]. The exact role of the wireless pressure capsule in the evaluation of children with possible colonic dysmotility is still under investigation.

High-Resolution Colonic Manometry

High-resolution manometry is a well-established tool in the evaluation of esophageal and anorectal motility. Similar technology has been developed for colonic assessment and has been tested primarily in adults [53–55] (Fig. 9.6). The spacing of the sensors is much closer with intervals as close as 1 cm as opposed to the greater than 5-cm spacing in the traditional water-perfused catheters. The recorded data is transmitted to a computer system with sophisticated software used in recording and analyzing the data. High-resolution colonic manometry has allowed the identification and classification of additional motor patterns in addition to

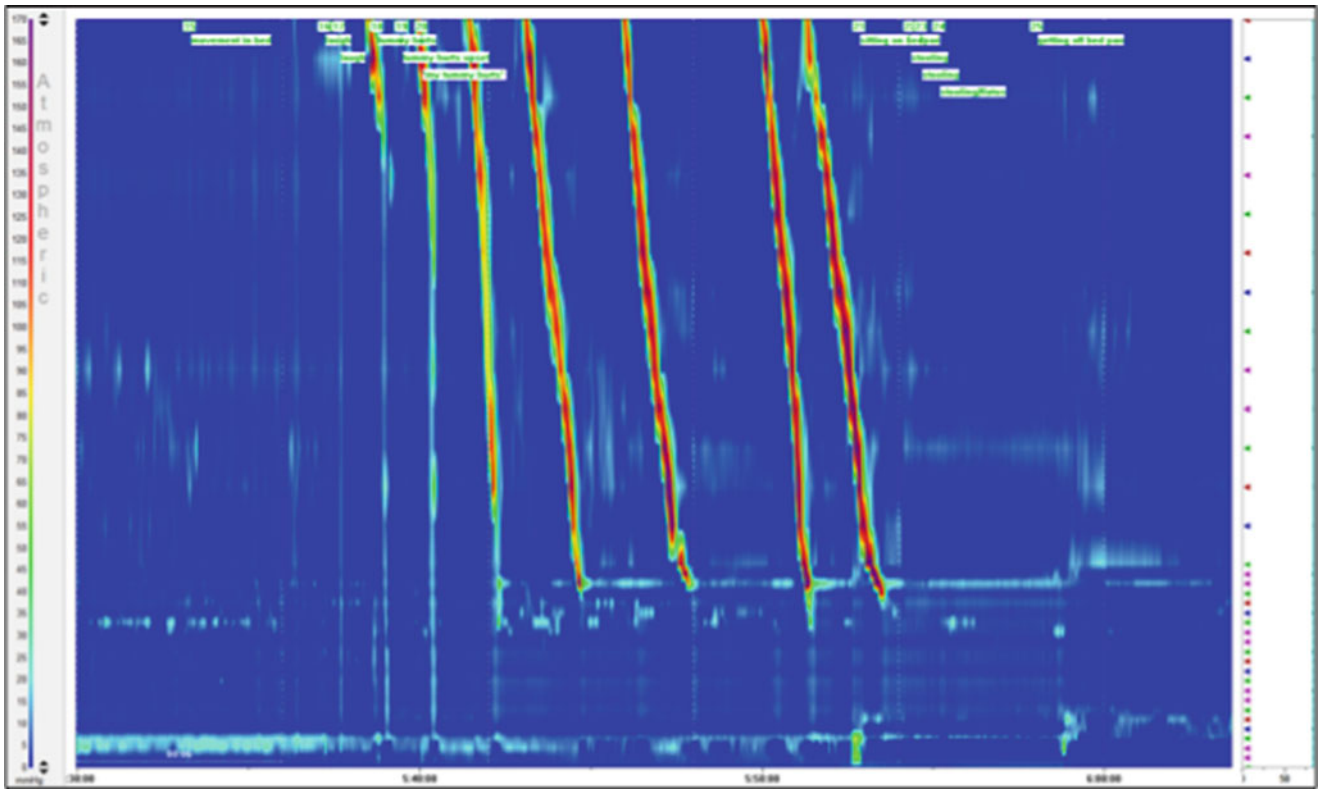

Fig. 9.6 A high-resolution pressure topography plot of colonic high-amplitude propagating contractions (HAPC) obtained using a 36-sensor solid-state catheter

the already well-described and well-studied HAPC. Some of these motor patterns were previously designated as non-propagating contractions, but studies conducted using high-resolution catheters with much more closely spaced pressure sensors have demonstrated that they do actually propagate over short distances and often in a retrograde direction [56, 57]. Additional prospective studies are needed to provide standards for the application of this technology and determine its utility in clinical practice.

Conclusion

Much information has been garnered in the field of colonic motility in the past decade, and pediatric studies have been at the forefront of clinical investigations. Colonic manometry has asserted itself as a standard diagnostic test in pediatrics and represents one of the rare instances of a manometric technique more commonly used in children than in adults. There are now clearly defined indications for its use and meaningful clinical decisions that are determined by its results. Colonic manometry is best performed in specialized centers by investigators with a special expertise in motility and who are comfortable in evaluating children with complex biopsychosocial disturbances. The technological aspects of how the test is performed and our ability to interpret the results continue to evolve. This evolution is accelerated by the introduction of new techniques, such as high-resolution fiber-optic manometry and wireless motility capsule.

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Anorectal Manometry

10

Claire Zar-Kessler and Jaime Belkind-Gerson

Anorectal dysfunction encompasses a variety of disease processes ranging from anatomical to functional abnormalities, which may lead to uncomfortable and distressing symptoms. Anorectal manometry (ARM) is used to obtain an objective assessment of symptoms and often aids in identifying disorders of defecation that cannot always be elucidated clinically. In pediatric patients, the test provides comprehensive information regarding anorectal abnormalities by evaluating the rectoanal muscle coordination, intactness and degree of sphincter tonic contractions, baseline reflexes, and subject perineal and internal rectal sensation. The most commonly evaluated symptoms in pediatrics are constipation and fecal incontinence. Disorders of defecation can be present at birth, while in other patients, it develops over time. Constipation and defecation abnormalities are common and account for approximately 3% of pediatrician visits [1]. While the incidence of pelvic floor disorders is unknown in the pediatric population, it can affect up to 10–15% of the adult population [2].

As several of the underlying disease processes including Hirschsprung disease, neuromuscular abnormalities, and dyssynergic defecation can have similar presentations but very different treatments, making the correct diagnosis is important. Anorectal manometry can help differentiate the different etiologies thus helping to guide appropriate therapy. In addition, the ARM can serve as an educational and therapeutic tool by providing information to patients and parents regarding the underlying pathophysiology of their symptoms.

Over the years, there has been progress in the available technology to perform anorectal manometry. For decades, the test had been executed using water-perfusion and sleeve catheter systems. In the past few years, there has been the introduction of both the high-resolution manometry (HRARM) and the 3D high-definition manometry (3DARM or 3DHDM), presenting us the ability to better investigate anorectal dynamics. We are now just beginning to elucidate how these newer systems may be used to expand our understanding, diagnosis, and treatment of patients with defecation disorders, particularly in pediatrics.

Normal Physiology

The pelvic floor is a striated muscular sheet that encloses the anorectum and urinary tract and in conjunction with the anorectal sphincters acts to maintain fecal continence and facilitate defecation [3, 4]. The anorectum is comprised of the union of the internal (IAS) and external (EAS) anal sphincters and the levator ani complex, including the puborectalis muscle, which forms a sling posteriorly, angulating the anal canal at rest [5]. The proximal, medial internal sphincter is formed by thickened circular smooth muscle innervated by the enteric nerves and thus under involuntary, reflexive control, while the distal, lateral external sphincter is comprised of skeletal muscle innervated by sacral nerves, under voluntary control. As the two sphincters are adjoining, they are frequently difficult to differentiate, particularly in younger patients in whom the sphincter size is very small [6, 7].

Continence is maintained at rest by a combination of sphincter pressure with the puborectalis contraction, together greatly exceeding the intrarectal pressure, thus preventing stool passage [8, 9]. The puborectalis muscle (PR), part of the levator ani muscle complex, is made of skeletal muscle. At rest it forms a sling around the anorectum producing an angle between 85 and 105°. By angulating the rectum, it helps to prevent stool passage and thus assists with continence at rest. Normal physiology has been assessed via ultrasound and MRI, strengthening our understanding of the complex area and the development of the area as a child grows [10].

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Defecation requires coordination of multiple muscle systems, involving contraction and relaxation at appropriate times to expel stool. In normal physiology, stool enters the rectum, distending the rectal walls and triggering a reflexive temporary relaxation of the internal sphincter, the rectoanal inhibitory reflex (RAIR) that elicits the urge to defecate. If the subject is not in an appropriate location to pass the stool, voluntary contraction of the external sphincter with persistent contraction of the puborectalis occurs, thus deferring defecation. Once defecation is deemed appropriate by the subject, expulsion of stool can be initiated. In healthy individuals with normal anorectal dynamics, this involves relaxation, contraction, and coordination of muscle systems. Specifically, the abdominal muscles contract to increase intra-abdominal pressure, propelling the stool forward from the rectum through the anal canal. At the same time, there is relaxation of the pelvic floor muscles including the puborectalis muscle, straightening the anal canal and allowing free passage of stool [11, 12]. Finally, both the external and internal sphincters relax, permitting stool to flow out of the canal and thus completing defecation.

Anorectal Manometry

Technical Aspects

There are two main compartments to an anorectal manometry system. These are the catheter or probe with a pressure-sensing apparatus and an inflatable balloon at its tip and the pressure-recording apparatus serving to amplify/record input, display information, and analyze data. Over the past decade, there have been significant advances in technology so that today there are multiple systems available for anorectal assessment, each with their own advantages and disadvantages. For years ARMs have been completed with basic performance systems including sleeve catheters, water-perfusion machines, and air-filled balloon catheters. Their use is now gradually being replaced with high resolution and 3D high definition. For the purpose of this chapter, the most commonly used systems will be reviewed including water perfusion, high resolution, and 3D high definition (Fig. 10.1).

The water-perfusion catheter consists of a flexible thin (diameter between 3.5 and 7.0 mm), plastic tube with four to eight side holes circumferentially or spirally arranged and a central catheter for balloon inflation. The catheter is connected to a perfusion apparatus with a pneumohydraulic pump set to pressures of 10–15 psi with water slowly perfused through the side holes at a rate of 0.1–0.5 mL/min/channel.

In 2007, with advances in technology, a high-resolution, solid-state manometric system was developed that has channels at 0.5–1.0 cm intervals. Each has multiple sensing points which together allow for retrieval of many (usually 36) data points producing a topographical plot of intraluminal pressure. This large amount of data retrieval provides a clearer visualization of the area and prevents loss of potentially important information. The results of the high-resolution catheter correlate well with the water-perfusion studies. Most recently, a 3D high-definition catheter was developed, producing even more accurate and detailed data retrieval. It is 10 cm in length and consists of 256 solid-state microtransducers placed circumferentially 3 mm apart. Due to the placement of these sensors, the results can be interpreted in a multidimensional fashion.

Since the creation of these systems, there has been much interest questioning if the newer modalities of anorectal manometry present added benefit over the older systems. When comparing the various catheter systems, the water-perfusion system has advantages in that it remains a low-cost option with ease of interpretation but can be difficult to calibrate and significant time is needed for maintenance of fluid channels. The newer technology with solid-state catheters has more sensors at closer intervals, thus providing significantly greater anatomic detail than prior systems, including a possible differentiation of the internal and external sphincter, which was not achieved previously [13]. The HRARM and 3DHDM are technically easier to use and, once placed in the appropriate position, do not require significant manipulation

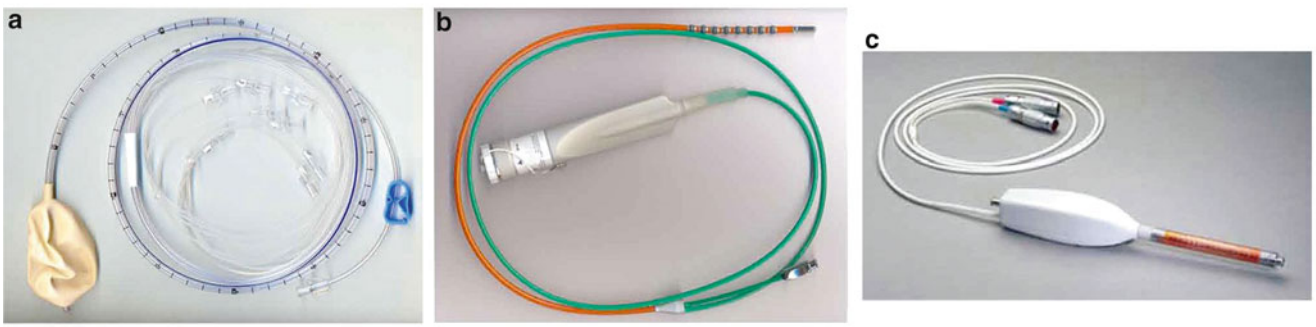

Fig. 10.1 (**a**) Water-perfusion catheter (Medical Measurement Systems). (**b**) High-resolution catheter (Medical Measurement Systems). (**c**) Three-dimensional high-resolution catheter (Sierra Scientific Instruments) (Courtesy of Medical Measurement Systems)

with minimal sensor migration, thus improving accuracy. Recently, the 3DARM has allowed for more detailed understanding of the anal canal anatomy. Specifically, it was used to construct a model of the anal canal pressures in pediatric patients noting the longitudinal and radial asymmetry of the anal canal. Thanks to this technology, it is now known that the EAS contributes to distal canal resistance, while PR and IAS contribute to proximal canal [14].

Although these newer probes are exciting, they are much more expensive, require significant time for cleaning, have a shorter life span, and are temperature sensitive. As the HRARM and 3DHDM are relatively new devices, their utility and practicality have not been fully established, particularly in the pediatric population. It is hypothesized that it may be helpful in further understanding the anatomy particularly in those with anatomical anorectal disorders and improved planning for procedures in this area [15]. Several ongoing studies are hoping to investigate if these newer technologies at an increased cost translate into clinical relevance.

Methodological/Practical Aspects

The ARM can be done in children of any age; however only children (usually 5 years and older) are typically able to cooperate with the sensory testing (external and internal) and dynamic components of the test (squeeze and bear-down maneuvers). Thus for younger patients, the ARM is usually limited to the analysis of anal sphincter resting pressure and RAIR. In preparation for an ARM, patients are encouraged to defecate and empty the rectal vault prior to the study. If there is a suspected large stool burden, an enema or suppository is used to prevent stool interference. Typically, as infants have soft stool and enemas may be traumatic at this age, no preparation is necessary [16]. It is suggested that medications that may interfere with function such as opioids or anticholinergics are held during the testing.

To set up for the exam, the patient is placed in the lateral decubitus position, with knees drawn to the chest, thus both hips and knees flexed passed 90°. A digital rectal exam (DRE) should be completed prior to the exam to evaluate the anatomy for abnormalities and gain a baseline assessment of the function of the area. It also provides a sense of the degree of stool burden and the extent of the patient's ability to follow commands which is necessary during the study. Adult studies have shown that the digital rectal exam can produce findings that are comparable to the results from the ARM [17]. Prior to the digital insertion, the perianal area should be examined along with assessment of external perineal sensation and anal wink. A finger is then inserted into the rectal canal to evaluate resting tone, squeeze pressure, and defecation dynamics including the presence of a paradoxical puborectalis contraction on bear down.

After completion of the DRE, a lubricated manometry probe is inserted into the rectum. Once placed and in the appropriate location, it is held there for at least 90 s for the anorectal area to acclimate to the insertion prior to obtaining data. It is important to provide clear and detailed explanations during the study as the clinician's verbal commands and clarifications have been shown to affect accuracy of results [18]. Helping the patient to relax by taking deep breaths or other techniques may be helpful in achieving a better baseline measurement.

Ideally the ARM study is completed in an awake patient without anesthesia or sedation, thus allowing voluntary and sensory testing. However, at times this is not feasible and anesthesia must be given, particularly in the toddler age. As above, one must be aware that this becomes a more limited study as these medications can alter the data. This should be accounted for when interpreting the study. It has been shown that ketamine and midazolam do not affect the sphincter pressure or RAIR response, while propofol decreases the resting sphincter pressure in a dose-dependent manner, although the normal RAIR is maintained [19–21].

Analysis

Baseline, dynamic, and sensory information can be obtained from an anorectal manometry study. Typically a complete study will assess sphincter pressure, bear-down maneuvers, sensation, and reflexes; however in specific situations, the test can be tailored toward particular questions. The following are the common assessments that are completed during the ARM study.

Resting basal pressure: After the patient is relaxed and comfortable with the probe in place, the basal resting sphincter pressure is obtained. This canal pressure measurement is comprised of mostly IAS tone (80 %) with some EAS pressure [22]. A low resting pressure could be indicative of weakness or disruption in the sphincter musculature. With the newer technology, the sphincter pressure can be measured with simple insertion of the catheter and obtaining data from the high-pressure zone. However, with water-perfusion manometry catheters, there are various methods employed. The most common of these is the station pull-through, when sensors are circumferentially arranged on the probe, or continuous withdrawal with spirally arranged sensors.

Squeeze: The squeeze pressure is used to assess sphincter strength/tone. It is produced by the patient voluntarily maximally tightening the anal sphincter and calculated as the highest pressure increase over the baseline resting pressure. This can be calculated as the average of three assessments. It is important to ensure that the intra-abdominal pressure is not increased during this exercise as it would alter the squeeze pressure data. A weak squeeze pressure may indicate myogenic or neurogenic causes (Fig. 10.2b).

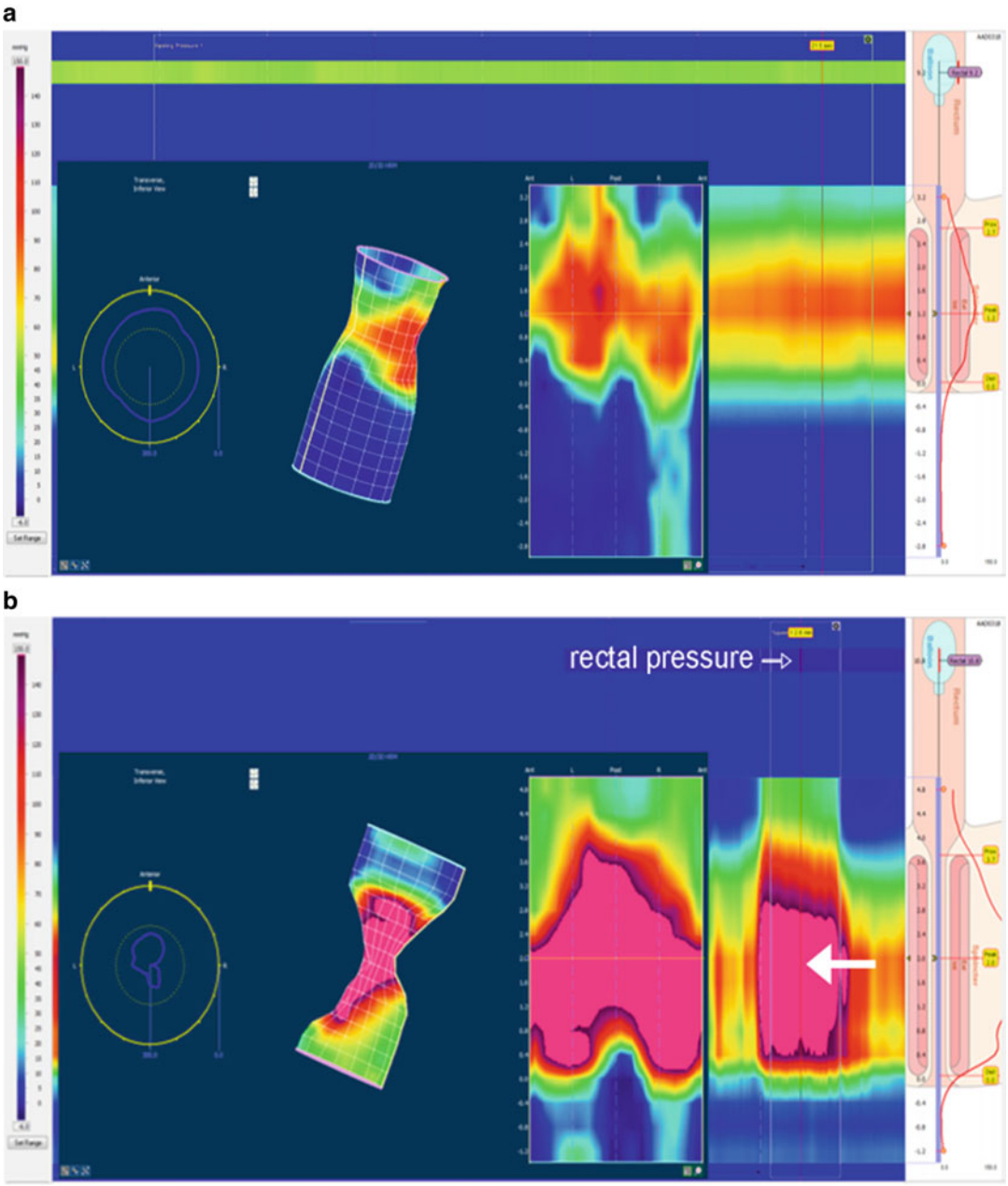

Fig. 10.2 (**a**) 3D: Resting (Baseline) anal canal during initial recoding. A moderate degree of increased sphincter pressure can be seen. This is often due to patient discomfort/anxiety. It is important to make sure the probe position does not cause discomfort and that the patient is allowed and encouraged to relax as much as possible. (**b**) 3D squeeze: Significantly increase pressure of sphincter (*large white arrow*), no pressure increase in abdomen and rectal balloon (rectal pressure, *open arrow*). (**c**) 3D bear down: Relaxation of the anal sphincter (*black arrow*), increase in pressure in the rectum (*white arrow*). (**d**) 3D dyssynergic defecation during bear down: Increased sphincter pressure (*white arrow*) in conjunction with only slightly increased rectal pressure (*black arrow*). (**e**) Paradoxical puborectalis: During the bear-down maneuver, a high-pressure area is seen above the sphincter (*white arrow*) in only the posterior aspect of the anal canal. This is the puborectalis sling which is not relaxing normally. The *black arrow* points toward the contracted sphincter which is below the puborectalis and is also seen in the anterior aspect of the canal

Anal canal length: The canal length is the measured distance between the anal verge and the location with ≥ 5 mmHg pressure increase over the rectal pressure.

RAIR: The rectoanal inhibitory reflex is obtained to assess the presence of the local enteric reflex. Most importantly, the absence of a RAIR suggests the presence of colonic

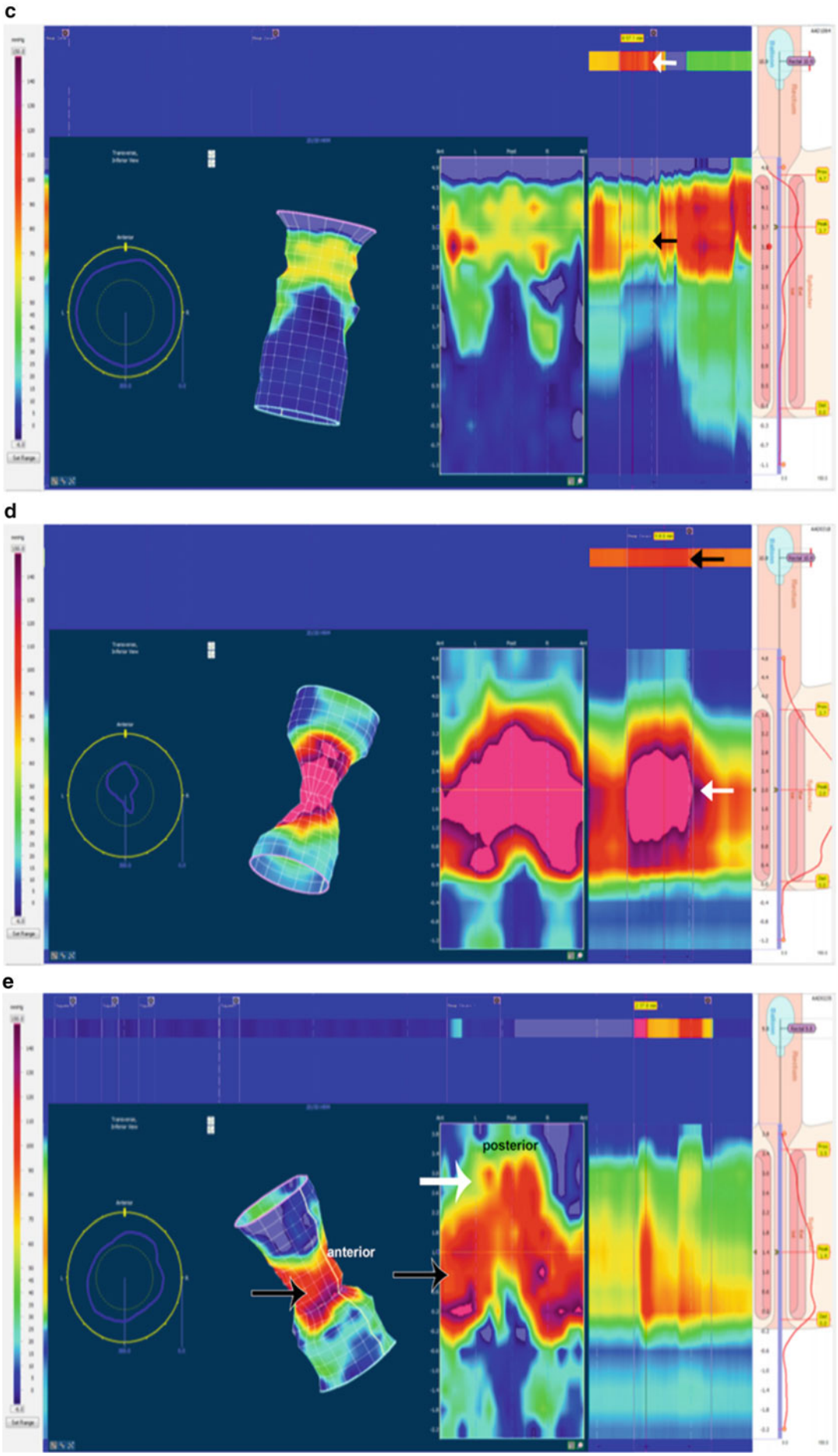

Fig. 10.2 (continued)

aganglionosis or Hirschsprung disease. The reflexive relaxation of IAS is naturally caused by stool presence but is simulated during an ARM by rapid balloon inflation and deflation. To date, in pediatrics there is no universally agreed criteria for the presence of a RAIR, which has previously been defined as either a drop in pressure by >5 mmHg or >15 % of the resting pressure. There is typically a dose-related response with greater relaxation and duration of relaxation with larger balloon volumes (Fig. 10.3a). When conducting the test, the clinician must be aware of possible migration of the catheter out of the sphincter, particularly during WPM. Catheter migration may falsely indicate a RAIR response when there is none (Fig. 10.3b). This is the most common cause of a false-positive RAIR (an apparent anal canal relaxation is seen but falsely produced by the catheter migrating in and out of the sphincter region/high-pressure zone with balloon inflation by lack of digitally securing the catheter to the anal margin). The most common cause for a false-negative RAIR test (there is no anal canal relaxation seen, despite balloon insufflation) is a dilated rectum, often due to chronic stool retention. As the rectum is dilated, the balloon does not reach the needed volume to adequately stretch the rectal wall, needed to elicit an anal sphincter relaxation.

Sensation: Testing the patient's sensation is an important part of the ARM exam as it provides additional information regarding the patient's perception of stool which can be indicative of anorectal dysfunction. Sensation is assessed in an awake, active participant (usually aged 5 years and older) by a gradual increase in balloon inflation size. First sensation is defined as the lowest balloon volume that is sensed by the patient. The urge sensation is the lowest balloon volume at which the patient develops the urge to defecate. Finally, the maximum tolerable sensation is the inflation size that is associated with severe urgency and pain. Decreased internal sensation is most often seen with a chronically dilated rectal canal due to persistent constipation.

Bear-down maneuver: The bear-down maneuver, or simulated defecation, is used to assess anorectal and pelvic floor pressure changes during attempted defecation. Similar to above, patients need to have the maturity to understand and cooperate with the testing. This ability is usually acquired around the age of 5 or 6 years. With normal defecation dynamics, there is an expected increase in rectal thrust pressure due to abdominal muscle contraction coordinated with a decrease in anal sphincter pressure. Patients in which these coordinated movements do not occur are thought to have dyssynergic defecation often resulting in outlet obstruction constipation [23]. Additionally,

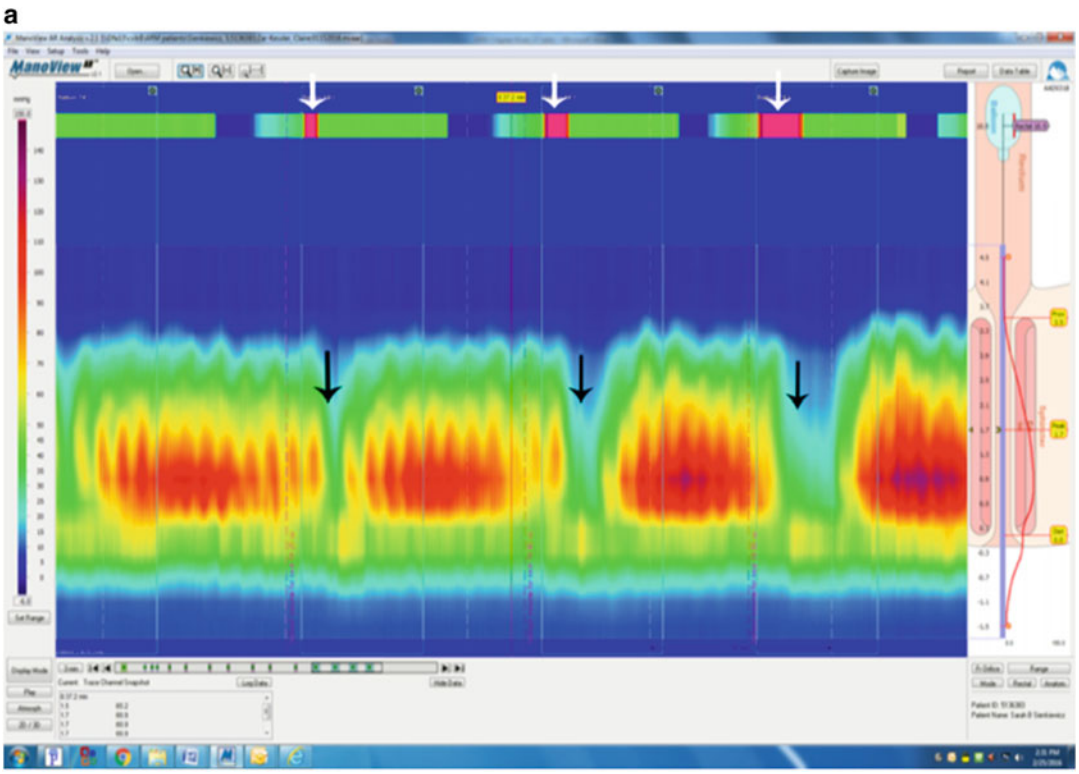

Fig. 10.3 (**a**) Dose-response RAIR 3D ARM. *White arrows* point to rectal balloon insufflation (which increases rectal sensor pressure). Anal canal relaxation (sphincter relaxation) is seen after each insufflation (*black arrows*). (**b**) WP RAIR. The *black arrow* signals balloon insufflation. The *red bar* was placed when catheter migration occurred, erroneously making the tracing appear as if anal canal relaxation had resulted from the balloon pressure on the rectum (seen in all four ports). This is a false-negative RAIR

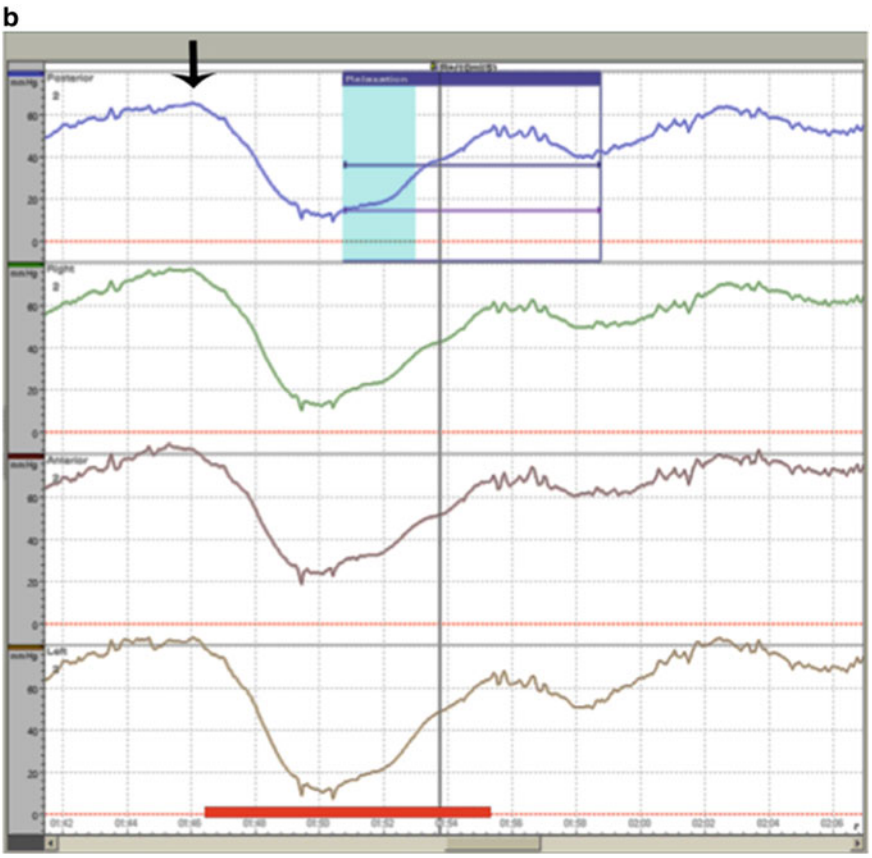

Fig. 10.3 (continued)

Table 10.1 References for normal manometric measurements

	Technique	Healthy controls, *N*=	Ages	Anal resting tone (mmHg)	Rectal pressure (mmHg)	Anal canal length (cm)	Threshold of RAIR (mL)	Sensation threshold (mL)	Critical volume (mL)	Maximal squeeze pressure (mmHg)
Benninga [10]	WPM	13	8–16 years	55 ± 16			18 ± 10	19 ± 12	131 ± 31	182 ± 61
Hyman [26]	Not specified	20	5–16 years	67 ± 12		3.3 ± 0.8				140 ± 52
		16	>5 years				11 ± 5	14 ± 7	101 ± 39	
Kumar [7]	WPM	30	<1 month (GA 34–39 weeks)	31 ± 11		1.7 ± 0.3	10 ± 4			
		30	1–16 months	42 ± 9		1.9 ± 0.6	14 ± 10			
		30	18 month to 12 years	43 ± 9		3.0 ± 0.5	25 ± 12			
Li [27]	Not Specified	10	5–15 years					28 ± 11	117 ± 46	
Sutphen [28]	WPM	27	~7–12 years					30 ± 12	96 ± 38	142 ± 47
Benninga [29]	Sleeve, WPM	22	Neonates (PMA 30–33 weeks)	32 ± 4[a]	9 ± 2		1.6 ± 0.3[b]			
De Lorijn [30]	Sleeve, WPM	16	Neonates (PMA 27–30 weeks)	25 ± 11[a]	7 ± 5		3.4 ± 1.6[b]			
Tang [31]	HRARM	180	Newborn (GA 28–42 weeks), 1–85 days old	29.7 ± 9.9		1.9 ± 0.5 cm				
Banasiuk [32]	3DARM	61	2–17	83 (23)		2.6 (0.68)	15.7 (10.9)	24.4 (23.4)		191 (64)

GA gestational age, *PMA* postmenstrual age
[a]Anal sphincter pressure
[b]Air insufflation

the puborectalis muscle can be visualized with the high-definition manometry, thus allowing for greater understanding of its contribution to defecation dynamics [24] (Fig. 10.2c).

Balloon expulsion: Once these assessments are complete, the probe is removed and a balloon expulsion test is performed. A balloon mounted on a plastic tube is inserted into the rectum and inflated to 50–60 cm^3. Some centers use air while others use saline to inflate balloon. The patient is then instructed to sit on a commode and expel the balloon in privacy. The test is considered normal if the patient is able to expel the balloon within a defined time. In adults 1 min is allowed. It is not clear if this time limit is adequate in pediatrics, as well as the right amount of balloon inflation for children, although one series reports that adult volumes and time limit may be applicable [25]. The balloon expulsion test is considered an adjunct evaluation to the ARM to confirm the presence of dyssynergia [25].

Overall, anorectal manometry has been found to be a safe test with rare side effects. With insertion of any foreign object, there is the risk of colonic perforation; therefore care should be taken with placement and removal of probes. Additionally, the study should be delayed or terminated with any abnormal symptom or sign including significant bleeding or acute onset of severe pain.

Reference Values

In general, reliable and reproducible normative values for anorectal manometry are lacking in pediatrics. Although baseline data has been reported in various publications, lack of standardization of the ARM study, a different methodology, and equipment make comparing these values a difficult endeavor [7] (Table 10.1). Therefore, as concrete normative data is lacking in pediatrics, it is always important to correlate the findings with symptom presentation.

The newer modalities of HRARM and 3DHDM have been studied more extensively in the adult literature, showing that the values with high-resolution manometry tend to be higher than those with water perfusion, and there may be differences based on gender, age, and BMI [33–36]. Data is just now being collected in the pediatric population with these modalities [31, 37]. In the future, as these newer systems are used more frequently and studied in more depth, a greater understanding of reference values both in symptomatic and healthy individuals is expected.

Indications

Hirschsprung: Hirschsprung disease is caused by the arrest of migration of the neural crest cells to the colon (see Chap. 25). The length of the aganglionic gut ranges from distal colon (most common) to complete colonic aganglionosis, sometimes even involving varying lengths of small bowel. Any length of colonic aganglionosis leads to an absent RAIR on ARM. Symptoms are frequently present in infancy with delayed passage of meconium (normally in first 24 h) and explosive stool output with digital rectal decompression. Patients may also present with constipation that is refractory to medication, signs of outlet obstruction, and, at times, failure to thrive. Most children are diagnosed within the first year of life, but there is a small subset of patients, particularly those with short-segment Hirschsprung disease that won't be brought to attention until later in life.

The absence of a RAIR on anorectal manometry has been shown to have a high diagnostic specificity and sensitivity for Hirschsprung disease, particularly in those older than 1 year [38, 39]. The gold standard for diagnosis is a full-thickness biopsy, but the anorectal manometry is a good alternative screening test as it is noninvasive and can often be completed without anesthesia. Patients with an absent RAIR should then proceed to a rectal suction or full-thickness biopsy to confirm the diagnosis.

Anorectal manometry can also be beneficial in postsurgical Hirschsprung patients to characterize the anatomy of the anorectal area, particularly as patients often have one or more surgical interventions and an altered anatomy [40]. Additionally, many patients with Hirschsprung disease continue to have symptoms postsurgically; the anorectal manometry can help to guide further management including additional necessary surgical interventions or medication therapy [41, 42].

Anal achalasia may easily be confused with Hirschsprung disease as the symptoms may be similar including chronic constipation, abdominal distention, and similar findings on ARM: high sphincter tone and non-relaxation of the sphincter with balloon inflation. However, these patients have a normal rectal biopsy [43, 44]. It is likely that anal achalasia is the disease previously known as "ultrashort-segment Hirschsprung disease." These patients are typically treated similarly to postsurgery Hirschsprung patients, as both the anal achalasia and the post-op Hirschsprung patients have a non-relaxing internal sphincter. Internal anal sphincter botulinum toxin injections have been very successful in improving defecation, although internal sphincter myotomy may be required in a subset of nonresponders [45, 46]. Thus, it is important to categorize these patients in order to provide them with the most appropriate therapy.

Neuromuscular: Patients with neuromuscular disorders such as myopathy or muscular dystrophy can frequently present with symptoms of anorectal dysfunction including constipation and fecal incontinence. Neuromuscular disorders can be evaluated with anorectal manometry to gain a further understanding of sphincter function in addition to the pelvic floor strength. Although there are no specific ARM findings, those

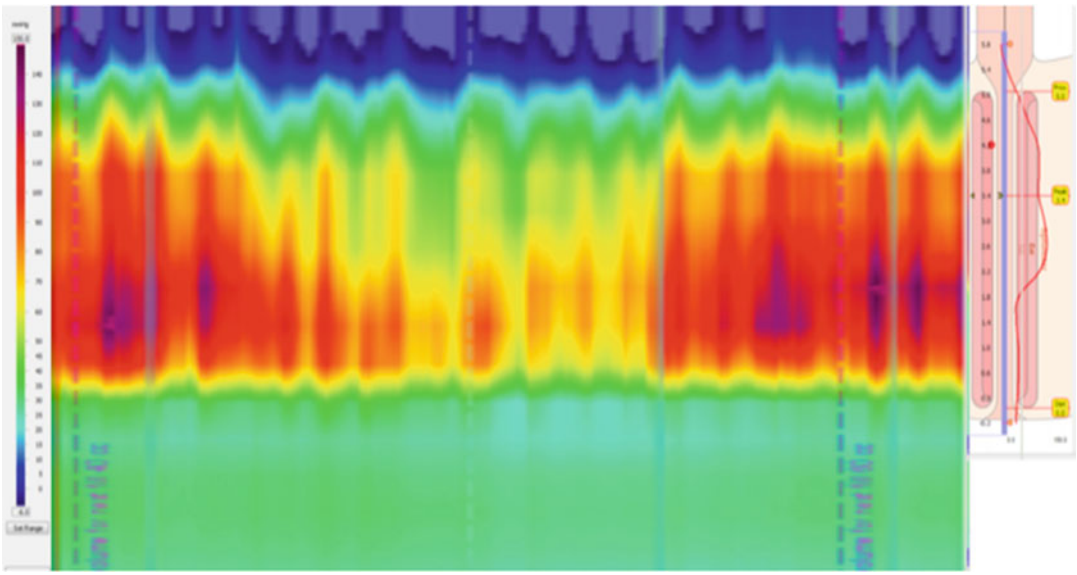

Fig. 10.4 Anorectal spasticity with balloon dilation seen with upper motor neuron dysfunction caused by a tethered cord

with neuromuscular diseases will frequently have hypotonia leading to low resting and squeeze pressures of the sphincter. There will be a RAIR response in these patients as the neurological reflex is intact, but the dose response to increasing inflation sizes may not be present [47]. Decreased muscular strength may also lead to decreased rectal thrust during Valsalva at the time of defecation. Patients with neuromuscular diseases and anorectal dysfunction can be difficult to treat as there are no medical interventions to reverse the disease process. These patients may respond well to conventional constipation therapy including laxative use and scheduled toilet use [48]. Physical therapy may help condition and exercise the striated muscles involved.

Anatomical: Structural abnormalities should be evaluated, particularly in those with postsurgical symptoms. For example, those with imperforate anus repair who remain symptomatic should have an ARM to assess postsurgical sensory and functional capabilities as these may remain abnormal even after the anatomy is repaired [49] (see Chap. 29). Additionally, patients who have undergone colostomy/diverting ileostomy and are preparing for reversal should have anorectal manometry completed to assess functioning of the area and rule out obstructed defecation prior to surgery.

Fecal incontinence: Fecal incontinence which includes both the passage of large bowel movements into the underwear in addition to slow leakage and streaking of the underwear can be further evaluated with an ARM study (see Chap. 43). Although fecal incontinence is frequently due to constipation, the ARM study, particularly the newer modalities, can be used to evaluate for other etiologies. For example, it may be able to show abnormalities in the anal sphincter functioning which can contribute to fecal incontinence. Additionally, spinal cord abnormalities such as meningomyelocele and tethered cord can affect innervation to the sphincter, altering its ability to aid in continence. As the spinal cord lesion may produce upper motor neuron abnormalities, there can be exaggerated contractions or anal spasms of the sphincter with balloon dilation and megacolon. In case of a lower motor neuron syndrome, decreased anal tone may be found. Patients with these suggestive findings on ARM should have an MRI completed to further examine the spinal cord (Fig. 10.4) [28, 50, 51].

Chronic constipation: Anorectal manometry can be used for evaluation in patients with chronic constipation (see Chap. 42). Studies have found that those with chronic constipation have specific anorectal manometry findings including increased frequency and amplitude of the internal anal sphincter contractions [52, 53]. As previously described, in order to appropriately pass stool, subjects need coordination of various pelvic and abdominal muscle systems. Some patients have abnormal movements in some or all of the muscle systems, leading to inappropriate muscle relaxation or contraction, thus complicating defecation [54]. This type of abnormality in defecation dynamics, called dyssynergic defecation, is thought to be the cause of some forms of constipation, particularly related to outlet obstruction [55]. Dyssynergic defecation can be classified according to abnormalities in three areas that can be assessed by anorectal evaluation during bear-down maneuvers including degree of perineal descent during defecation, perineal location at rest, and anal resting pressure [56]. These findings of dyssynergic defecation can be confirmed via an abnormal balloon expulsion test. Newer technology has provided a

deeper understanding of anorectal dysfunctions and has helped to identify phenotypes in defecatory disorders and fecal incontinence in addition to providing improved classification of the puborectalis muscle and its role in outlet obstruction [24, 57].

In adult patients, the phenotypic characterization of dyssynergic defecation has been classified into the following four categories related to combinations of rectal thrust in addition to anal canal relaxation [58]:

Type 1: paradoxical increase in anal pressure with increase in rectal pressure (>40 mmHg).
Type 2: paradoxical increase in anal pressure without increase in rectal pressure (<40 mmHg, poor propulsive force).
Type 3: adequate increase in rectal pressure with failed reduction in anal pressure (no anal relaxation) (<20 % baseline pressure).
Type 4: inadequate increase in rectal pressure with failed reduction in anal pressure.

Type 4 is the only one that differentiated between healthy volunteers and those with functional constipation [59]. While it is likely that these rectoanal dynamics are similar, it is not currently known whether this classification applies and is useful in children.

Dyssynergic defecation has been treated with biofeedback with varying success in the pediatric population [48, 60]. Using sensors and guidance via animated games, patients are taught to appropriately relax the pelvic floor and sphincters while increasing abdominal pressure. The intention is that with improved muscle coordination, the patient will be able to expel stool more efficiently, decreasing the rectal stool burden.

Anorectal manometry can be used both to diagnose dyssynergic defecation and to guide specific biofeedback treatment, including targeting the puborectalis muscle. Recently, it was found that many healthy adults were found to have dyssynergic patterns of defecation using the 3DHDM. This is hypothesized to be in part related to the larger size and less flexibility of the probe thus possibly stretching the sphincter, leading to decreased accuracy in the results [59]. Therefore, this discrepancy must be taken into account when using the 3DARM system to analyze patients [59], particularly until more data is available in pediatrics.

Conclusion

Anorectal manometry is a safe and well-tolerated procedure that provides valuable information regarding the underlying anatomy and functionality of the anorectal canal. Many pediatric patients have varying symptoms consisting of constipation and/or fecal incontinence which are debilitating and embarrassing. Anorectal manometry can be used to differentiate several of the disease processes that may present with similar symptoms but require different treatments including Hirschsprung disease, spinal cord lesions, neuromuscular disease, and dyssynergic defecation. In recent years, newer technology has been introduced that has allowed us to better describe the anorectal canal and understand anorectal pathology including asymmetric sphincter pressure and types of dyssynergic defecation. However, as these modalities are relatively new, their clinical utility and superiority over prior testing modalities have yet to be determined in pediatrics. In conjunction with correlation to a patient's symptoms, anorectal manometry is a useful tool to understand the pathophysiology of specific disease entities and for determination of appropriate interventions and treatments. With time, there is anticipation that the clinical usefulness of the newer modalities including 3DHDM and HRARM will be clarified and appropriately implemented.

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Assessment of Feeding and Swallowing Disorders

11

Nathalie Rommel

Maturation of feeding skills, fine motor coordination of swallow musculature, and adequate sensory development are key components to develop safe, effective, and efficient swallowing with airway protection and full bolus clearance from the oropharyngeal segment [1–3]. In case of oropharyngeal dysphagia, one or more of these contributing systems may be dysfunctional. The relationship between clinical presentation and underlying cause of feeding problems is often unclear and relates to the fact that similar signs or symptoms may reflect different etiologies. Because of this lack of a one-to-one correspondence between clinical presentations and underlying causes of dysphagia, careful identification of symptoms, documentation of their pathophysiology, and their relation to the mealtimes is crucial in pinpointing the specific cause of feeding disorders. It is nowadays accepted that feeding difficulties in infants and children need to be assessed from multiple perspectives in order to determine the underlying causes. A multidisciplinary approach has been described, leading to better identification and treatment of feeding and swallowing disorders [4]. This chapter describes the clinical as well as most commonly used instrumental techniques that are available to diagnose pediatric patients with dysphagia. The clinical value of these diagnostic tests and their sensitivity to predict outcomes remain however often unclear. Despite considerable clinical research efforts, conventional diagnostic methods for pediatric oropharyngeal dysphagia have limited proven accuracy in predicting aspiration and respiratory disease.

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Assessment of Oropharyngeal Dysphagia

The assessment of oropharyngeal dysphagia should consist of two major components: the first one is direct observation of the child's feeding and swallowing skills through clinical oral assessment. The second part is assessing the not-visually obvious motor function of pharynx and esophagus through instrumental testing.

Clinical Assessment

The main goal of the clinical oral assessment is to define the underlying cause and the severity of the feeding and swallowing difficulties. In this problem-solving process, the evaluation of the oral cavity and its functions by observation plays a major role. During the clinical assessment, the oral anatomy, motor skills, reflex activity, responsivity, and swallowing are examined, and the nature of the feeding problem and necessity for further evaluation of pharyngeal swallowing function with instrumental techniques is established. Normal and abnormal oral motor skills have been described extensively in many anatomy textbooks, as well as in the developmental and rehabilitation literature [5]. A recent overview published by C. Lau [6] describes the evidence-based research of the past two decades on the development of very-low-birth-weight infants' oral feeding skills. The article provides different functional levels that relate to the child's inability to feed by mouth safely and competently [6]. In order to feed successfully, a child must adapt to the tactile characteristics of tools (breast, bottle, spoon, or cup) and food so that the correct motor responses are performed [7]. Oral motor and sensory-based feeding disorders can be differentiated [8], and a structured sensory examination in and around the oral cavity allows the examiner to uncover difficulties with the tactile components of feedings. However, it is only possible to observe the reactions to sensations, not

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the sensations in themselves [9, 10]. Therefore the term responsivity is more appropriate than sensitivity in the context of dysphagia. The child's ability to respond adequately to tactile input can be assessed during a feeding observation or by a structured sensory examination by grading the sensory input. A sensory baseline on consistency, taste, temperature, tools, area of stimulation, and amount needs to be established, defined as the level of tactile input that the child can tolerate without any discomfort. A wide range of tactile responses can be observed, and these responses form a continuum of function: aversion, hyperresponsivity, normal tactile responses, hyporesponsivity, and absent responses [7]. When tactile responses are severely diminished or absent, a significant sensory impairment should be suspected which can hinder oral feeding. In hyporesponsivity, strong stimulation is required and the responses are slow or partial. A hyperresponse is exaggerated or out of proportion to the strength of the stimulus. While similar to hyperresponses, aversive responses are even stronger and more negative. Both hyperresponses and aversive responses can be part of a general tactile processing problem or be localized to the face and mouth or even more specifically to a certain part of the mouth, most frequently the tongue [11].

To structure the oral feeding and swallowing assessment, a clinical assessment scale or checklist for pediatric dysphagia can be used. Many scales have been provided; however, only few have a sound theoretical merit [10]. A systematic literature review on the available noninstrumental assessment scales for feeding and swallowing in the pediatric population has been published in 2016 [12]. The authors confirmed that information on the validity and reliability of these assessment scales is scarce hence emphasize that psychometric analysis of the used clinical assessment scales is needed to avoid incorrect interpretation and inconsistent use [12].

During the examination the clinician will also determine whether the parent's reports and perceptions match the observations by the clinician [13]. Referrals can then be made for further assessment or multidisciplinary management and a targeted treatment plan can be developed.

Instrumental Testing

Instrumental assessment has the potential to assess oropharyngeal function objectively if selected and applied properly. A variety of clinical and instrumental diagnostic techniques are used. Each technology has strengths and limitations, and the specifics of each diagnostic method have been extensively described for use in adults [14, 15]. This section will discuss the most commonly used gold standard and some emerging evaluations for diagnosing pediatric patients with dysphagia within a multidisciplinary context.

When supplemental instrumental assessment of the pharyngeal swallow is required, a variety of pharyngeal and UES dysfunctions can be distinguished. The pharyngeal pathology varies from synchronous pharyngeal peristalsis, pharyngeal focal failure, pharyngeal hypocontractility, and pharyngeal paralysis. Upper esophageal sphincter patterns range from a normally relaxing UES to premature contraction to an incomplete or non-relaxing UOS in case of achalasia. How these deglutitive patterns are linked with aspiration risk remains unclear.

Common assessment techniques available for use in the pediatric population include fiberoptic endoscopic evaluation of swallowing (FEES), videofluoroscopy, and pharyngeal-esophageal manometry. In practice, the use of a particular instrumental technique often depends on the institutional experience, available resources, and its commercial availability rather than being based on the performance characteristics of the test. The main argument of using instrumental techniques in addition to clinical examination is to provide a more precise understanding of the biomechanics of the child's swallow which then will lead to a more targeted therapeutic intervention [16]. The challenging decision is when to refer for instrumental assessment and for what type of testing.

Videofluoroscopy

Videofluoroscopic swallow study or modified barium swallow has been considered the diagnostic study of choice to evaluate oropharyngeal swallowing anatomy and physiology for many years now [4]. Videofluoroscopy is a dynamic continuous radiological examination of the anatomy and function of the oral cavity, pharynx, and UES opening that includes lateral and frontal views while swallowing a high-density barium or non-ionizing contrast bolus of different consistencies. This test examines oral and pharyngeal regions with the child seated in an upright or semi-reclined position [17]. Once the swallow disorder is identified, postural or therapeutic interventions can be suggested to reduce the swallowing problem [4]. The entire examination is recorded for review afterward.

The main reason for referral for videofluoroscopy is aspiration risk [18]. The most widely used validated scoring system to assess the presence and severity of aspiration and penetration in relation to swallowing is the Penetration–Aspiration Scale [19].

Videofluoroscopy has limitations, such as the need for ionizing radiation and thereby the reluctance to repeat the procedure, the child unfriendly environment of the radiology suite, and the mainly qualitative nature of information obtained. However, with some custom-made software programs, it is feasible to derive numerical measures such as the timing of opening or closing of the velopharyngeal junction, laryngeal entrance, and upper esophageal sphincter, which

provides information on airway protection mechanisms and can be used to assess aspiration risk [20, 21].

Quantitative fluoroscopy measures such as, and more so in pediatrics, these are not routinely collected in clinical practice, presumably because they are considered time consuming. Patients are not usually referred for fluoroscopy until they have deteriorated clinically with symptoms. In pediatrics fluoroscopy is, as in adults, mainly used as an assessment method for symptomatic patients, with repeated fluoroscopy only performed occasionally because of the radiation exposure and evidence that fluoroscopy is a fairly poor predictor of development of aspiration pneumonia [18, 22]. Videofluoroscopy with manometrical evaluation has become more commonly used and is indicated to rule out the specific cause of deglutitive aspiration, to assess the presence and impact of pharyngeal dysfunction and upper esophageal sphincter function or in case there is no therapeutic progress 2 months after the initial videofluoroscopy. In other words, videomanometry is used to provide biomechanical and quantitative explanations for the radiological findings as well as for patient symptoms of abnormal pharyngeal bolus transport [22].

Fiberoptic Endoscopic Evaluation of Swallowing (FEES)

In fiberoptic endoscopic evaluation of swallowing (FEES), a flexible laryngoscope is used to view pharyngeal and laryngeal structures before, during, and after deglutition [23, 24]. During the test, the endoscope is introduced transnasally and advanced to enable visualization of the mucosal surface and movement of the tongue base, pharynx, and larynx, as well as the bolus transit and airway protection. During the normal swallow, a white-out period of ~0.5 s occurs at the time of epiglottic tilting and maximal pharyngeal closure, which prevents viewing of the entire swallow [24]. During the examination, the patient swallows a variety of foods and liquids with a coloring contrast (blue dye or milk) added to maximize visualization of the bolus. FEES provides visual feedback on aspiration and penetration, qualitative information on morphology, presence of secretions and residue, the timing of the swallow onset, and clearance of residue. FEES is a commercially available diagnostic system and, over the past 15 years, has been used to evaluate swallowing in relation to aspiration and penetration [25], head posture [26], and bolus type [27–29], but few report focus on children in children [30]. Those published pediatric studies report, however, the FEES procedure as well tolerated and safe with no respiratory distress or cyanosis during or after the procedure [31–35], repeatable and, as it is portable, can be performed at the bedside [31]. The limitations of FEES are that it does not allow quantification of the swallow physiology and relies on subjective interpretation of findings such as residue.

Manometry and Impedance

Manometry can be used to assess pharyngoesophageal motor function such as pharyngeal weakness or impaired UES relaxation [36] and has been used to describe alterations in pressure patterns in relation to age-related changes, neurodegenerative disease, postsurgical dysfunctions, and UES obstruction [37–39]. However, while manometric recordings may identify functional abnormalities that may predispose to aspiration risk, manometry on its own cannot predict circumstances when aspiration is likely. Therefore, intraluminal impedance has been explored as a technique that can be used to detect failed bolus transport for its use to assess swallow function as is easily combined with manometry. The widespread application of impedance measurement to assess the pharyngeal function has been slow to develop because attempts to establish criteria that reliably identify post-swallow residue have been largely unsuccessful [40–42].

Manometric and impedance technologies have evolved in recent years such that catheters with closely spaced pressure-impedance arrays are more widely available. Over the last 5 years, high-resolution manometry with impedance (HRMI) with automated Pressure Flow Analysis (PFA) has been suggested as a new method to diagnostically interpret pharyngeal and UES function [43]. Pressure sensors measure activity of swallow musculature, while impedance electrodes provide metrics which indicate bolus flow. In adults as well as in pediatrics, PFA derives a range of swallow metrics that indicate contractile vigor, intrabolus pressure, bolus presence before and after the swallow, bolus flow timing, and UES diameter and thereby delivers a nonsubjective evaluation of different mechanical components of pharyngeal swallow [44]. A global swallow risk index (SRI) generated from PFA metrics as a means to amplify dysfunction has shown in adults as well as in children to correlate with the presence of aspiration and/or post-swallow residue as seen on videofluoroscopy [4, 43, 45]. Figures 11.1, 11.2, and 11.3 illustrate a normal pharyngeal swallow and that with dysphagia both on radiology and on high-resolution impedance color plot.

Summary

Regardless of the primary medical pathology, it is crucial to assess the core biomechanics of swallow physiology with assessment techniques which are as objective as possible. Incorporation of measurable objective assessments into clinical diagnosis is needed and might be key in developing novel therapeutic strategies for infants and children with dysphagia. Recent advances using different instrumental technologies are promising and need ongoing validation in the pediatric population.

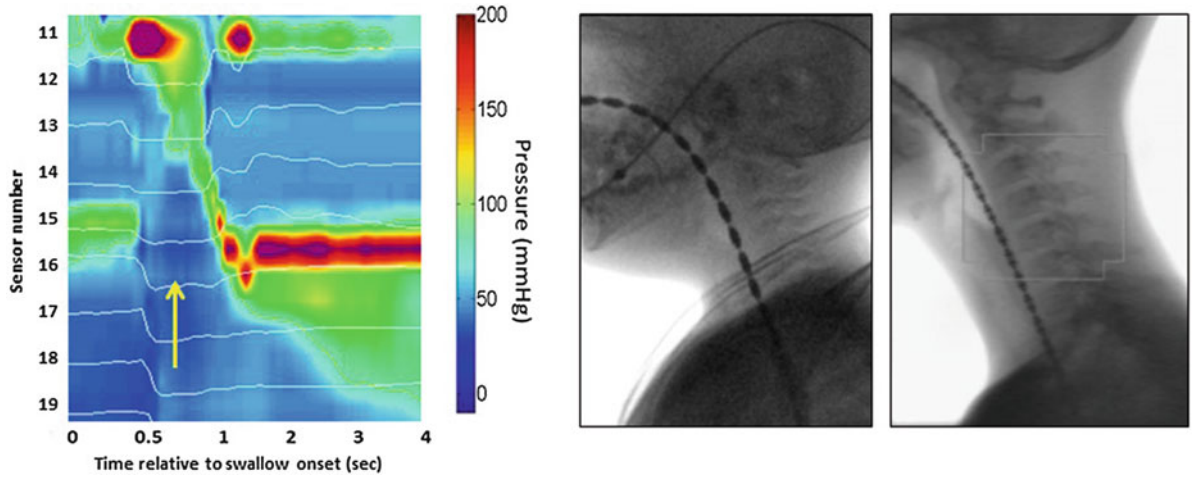

Fig. 11.1 (**a**) HRM color plot of a normal liquid swallow in a 5-year-old child. Pressure is an indication according to color code illustrated. (**b**) Lateral radiological view of the pharynx and UES showing the transnasal placement of the HRM solid-state catheter in a 5- and 11-year-old child

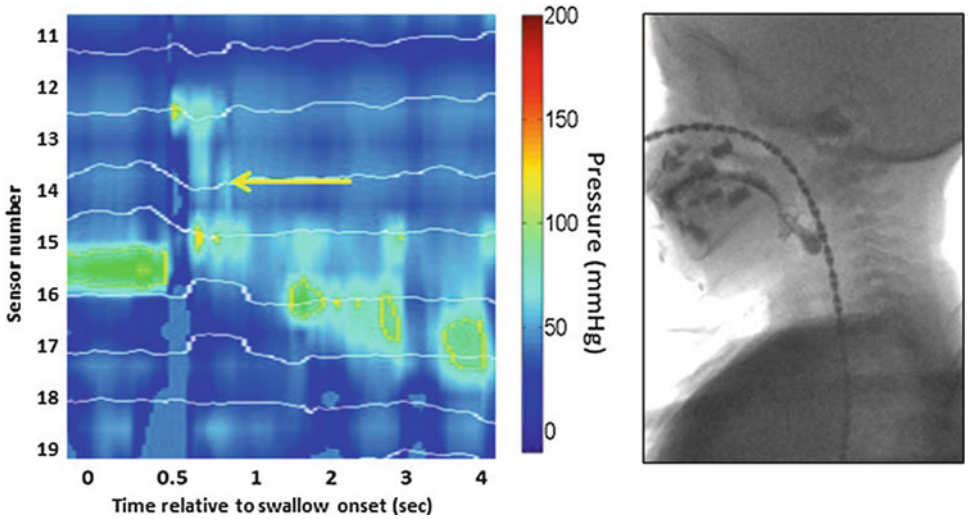

Fig. 11.2 HRM plot illustrating adequate UES relaxation and a hypocontractile pharynx in a 2-year-old patient presenting with dysphagia on liquids. Radiology shows post-swallow residue in the piriform sinus and poor UES opening secondary to poor pharyngeal bolus propulsion despite complete UES relaxation

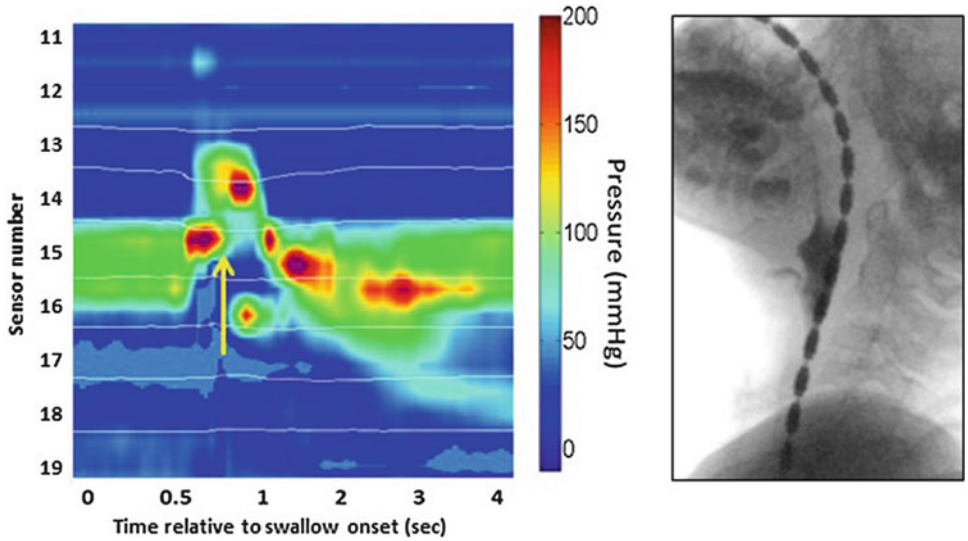

Fig. 11.3 UES dysfunction in a 4-year-old girl with CP presenting with chronic dysphagia and recurrent aspiration pneumonia. Increased pharyngeal intrabolus pressure as a result of resistance to bolus flow across a non-relaxing UES. This example illustrates that intrabolus pressure can only occur when pharyngeal pressures are intact. Naso-oropharyngeal contractions fail in this patient and intrabolus pressure cannot be determined

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Esophageal pH and Impedance Monitoring

12

Eric Chiou and Rachel L. Rosen

Gastroesophageal reflux disease (GERD) is distinguished by the reflux of gastric contents into the esophagus resulting in well-defined symptoms and complications [1, 2]. In many cases, GERD can be diagnosed based on history alone; however, when patients present with atypical complaints or do not respond to medical therapy, objective testing may be necessary to assess the frequency and duration of acid reflux, or to document the association between gastroesophageal reflux (GER) and specific symptoms [3]. Diagnostic techniques designed to discriminate between physiologic and pathologic reflux have been developed.

Esophageal pH monitoring, which employs a pH electrode to detect acid reflux in the distal esophagus, was first introduced in 1969 [4]. Over the years, the advantages and limitations of traditional, catheter-based esophageal pH monitoring have become better defined, with a subsequent evolution of newer diagnostic techniques. Wireless methods to detect acidic contents in the esophagus have now become available (Bravo pH capsule). Additionally, we have seen the development of the technical capability of measuring both acid and nonacid reflux with multichannel intraluminal impedance. In the present chapter, we will discuss the technical details, clinical indications, and applications of these diagnostic techniques for the dynamic detection of reflux episodes.

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Catheter-Based Esophageal pH Monitoring

Catheter-based esophageal pH monitoring is the most widely available and commonly used method to document abnormal acid exposure and correlate symptoms with acid reflux episodes. Testing quantifies the frequency and duration of acid reflux episodes, usually over a 24-h period. Most ambulatory catheter-based pH probes contain a small antimony electrode attached to a portable data logger that records intraesophageal pH as well as events during the study such as symptoms, meals, position changes, and activity. The methodology of esophageal pH monitoring has become relatively standardized with specific guidelines for use in children [3, 5].

Electrode Placement

Appropriate placement of the pH electrode relative to the LES is very important for accurate data. At higher and higher locations above the LES, there is a linear decrease in acid exposure time, which decreases the sensitivity of the test. Adult protocols typically recommend that the pH electrode be positioned 5 cm above the superior margin of the lower esophageal sphincter (LES) in order to decrease the risk of slipping into the stomach during swallow-induced shortening of the esophagus [6]. Stationary esophageal manometry, usually performed as a separate procedure, is optimal for determination of LES location. In children, however, this additional invasive procedure is usually not performed. Strobel's formula may be used to approximate the esophageal length for initial placement of the pH electrode above the LES [length from nares to LES (cm) = 5 + 0.252 (height)] [7]. In the absence of manometry, however, fluoroscopy or chest x ray should be used to confirm placement of the sensor at the level of the third vertebral body above the diaphragm based on recommendations from the Working Group of the European Society of Pediatric Gastroenterology and Nutrition [5].

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Recording Conditions

The optimal duration of monitoring should be at least 18 h, including a day and a night period [5]. Instructions for feeding and activity during the study should represent a balance between maintaining a degree of standardization and recreating normal circumstances with minimal restrictions. Although a strict standardized diet is generally not necessary, a minimum of three meals should be included. Investigators may consider excluding meal times from analysis, since it is difficult to distinguish episodes of GER from pH changes secondary to swallowing acidic foods from true reflux. Documentation of patient position and activity during the study should also be recorded since the effect of body position on different patterns of GER has been well reported [3]. Depending on the aim of the study, H_2 blockers and proton-pump inhibitors should be stopped at least 3 or 7 days prior to the study, respectively [6].

Definitions and Criteria

After the study is completed, data is downloaded from the data logger and analyzed with computer software. A pH of 4 is generally accepted as the optimum cutoff in both children and adults, based on early studies of correlating acid exposure with heartburn [8]. The threshold of pH < 4 also provides the best discrimination between subjects with proven reflux disease and asymptomatic controls [3, 6]. A reflux episode is usually defined as a drop in pH below 4 that lasts for more than 5 s [9]. The reflux index (RI), which is the percentage of time of the entire duration of the investigation with pH < 4, is generally considered the single most important variable in clinical practice for both adults and children [3, 6].

Normal Ranges

Normative data are essential to guide interpretation of pH monitoring results and distinguish between physiologic versus pathologic reflux. Published pediatric data is rather limited, however, due to the difficulty in obtaining data from truly healthy and asymptomatic volunteers. In some studies, "normals" were obtained from children hospitalized for GER evaluations who turned out to be asymptomatic during the time of pH monitoring [10] or were found to have other causes for their gastrointestinal symptoms [11]. Overall, studies suggest that physiologic acid reflux is a common occurrence in infants during the first year of life, with decreased acid exposure found in older children and adults [10–14] (Table 12.1). Based on the available data, the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and European Society Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) jointly recommended that normal ranges should be used as guidelines for interpretation rather than absolute "cutoff" values; in pH studies performed with antimony electrodes, an RI > 7 % is considered abnormal, an RI < 3 % is considered normal, and an RI between 3 and 7 % is considered indeterminate [15].

Diagnostic Accuracy and Reproducibility

The sensitivity and specificity of pH monitoring for the diagnosis of GERD in children are not well established. pH monitoring appears to be a good predictor of esophagitis in children, with sensitivity ranging from 83 to 100 %; on the other hand, the severity of reflux as measured by pH monitoring correlates poorly with the severity of symptoms, especially in infants [3, 16]. For children with non-erosive reflux disease, the clinical utility of pH monitoring has not been well studied.

Reports on intrasubject reproducibility of esophageal pH results in children have had varied results. Vandenplas et al. studied infants and children over two consecutive 24-h periods; the correlation coefficients for the reflux index and number of reflux episodes between days 1 and 2 were 0.95 and 0.98, respectively [17]. In contrast, the correlation coefficient for the reflux index reported by Mahajan and colleagues was only 0.62 between days 1 and 2 [18]. In another

Table 12.1 Esophageal pH data from asymptomatic infants, children, and adults (mean upper limit of normal = mean + 2SD)

Reference	*n*	Mean age (range)	Number of reflux episodes/24 h	Reflux index (% time pH < 4) (%)
Infants				
Vandenplas et al. [14]	509	2 months (0–11 month)	73	11.7
Children				
Boix-Ochoa et al. [10]	20	19 months (2 months–3 years)	27	5.1
Sondheimer [13]	6	61 month (1–24 months)	22	2.7
Euler and Byrne [12]	22	15 months (1–108 months)	14	3.1
Cucchiara [11]	63	24 months (2 months–12 years)	28	3.4
Adults				
Vitale et al. [105]	50	25 years		7.2
Richter et al. [106]	110	38 years		5.8

study, 9 out of 30 children had discordant (normal versus abnormal) results between the two recording days, yielding an overall reproducibility of 70 % [19]. Overall, there appears to be some degree of day-to-day variability among patients; whether these differences are clinically significant is debatable. When the clinical picture is unclear, consideration should be given for repeat testing.

Symptom Correlation

In addition to the quantification of reflux, 24-h esophageal pH monitoring also provides the opportunity to assess the temporal relationship between episodes of reflux and onset of symptoms. This may be especially helpful for patients with nonspecific or extraesophageal symptoms. Lam et al. found that using a 2-min time window was best for correlation of chest pain with reflux, although the optimal time window for symptom-reflux association may vary depending on the particular symptom of interest [20].

Several statistical methods have been developed to better quantify the association of symptoms and reflux episodes, but there is no conclusive data proving one index to be superior to the others. The symptom index (SI) is defined as the percentage of symptom episodes that are related to reflux, with a score of ≥50 % suggesting a positive relationship between symptom and reflux [21, 22]. A second approach is the symptom sensitivity index (SSI), which divides the number of reflux episodes associated with symptoms by the total number of reflux episodes [23]. An arbitrary cutoff of 10 % or higher is commonly used to indicate a significant association between symptoms and reflux episodes. Both the SI and SSI fail to integrate, however, all the factors determining symptom correlation. As a result, the SI may overestimate the relationship between reflux and symptoms when there are a high number of reflux episodes, and the SSI is more likely to be positive when the number of symptom episodes is high. More recently, the symptom association probability (SAP) was introduced. Using Fisher's exact test, this method expresses the statistical likelihood that the patient's symptoms are related to reflux [24]. By statistical convention, SAP ≥95 % indicates that the probability that the observed association between reflux and the symptom occurred by chance is <5 %.

Although patients with a positive relationship between symptoms and reflux have been shown to more likely to respond to medical and surgical therapy, further prospective validation studies are needed [25, 26]. Ultimately, these indices may be helpful in evaluating the relationship between symptoms and reflux, but a statistically significant result does not necessarily imply causality.

Wireless pH Monitoring

To overcome the limitation of patient discomfort seen with catheter-based pH monitoring, a wireless method is also available. The Bravo pH system (Medtronic, Shoreview, MN) consists of an antimony electrode contained within a small capsule which is securely pinned to the mucosal wall of the distal esophagus and transmits pH data wirelessly to a portable receiver using radio telemetry. In adults, the capsule is placed 6 cm above the squamocolumnar junction, with placement confirmation by endoscopy [27]. There are currently no specific guidelines for placement in children.

In published studies of children older than 4 years old, pH monitoring with the Bravo capsule was better tolerated than the trans-nasal catheter in terms of appetite, activity, and satisfaction, with no significant complications other than mild chest discomfort [28–30].

Another advantage of the Bravo system is the ability to perform prolonged monitoring over a 48-h period, which has the potential for maximizing time for symptom-reflux correlation and reducing the overall miss rate for days where pathologic acid reflux may be present. There are no outcome data however proving that a 48-h study is better than 24-h monitoring for predicting response to treatment in either adults or children. Furthermore, given the need for sedation for capsule placement on day 1, there has been concern about the reliability of day 1 data. Adult studies comparing days 1 and 2 of wireless pH have shown variable results, with some studies reporting no difference in reflux between days 1 and 2 [27], while others have reported increased reflux on day 1, and still others showing increased reflux on day 2 [31, 32]. Similarly conflicting data has been reported in children. Some studies have reported no significant difference in pH measurements between days 1 and 2 [33]. In Cabrera et al., there was also no significant difference between reflux index recorded on day 1 versus day 2 overall; however, for 9 % of patients, the reflux index was normal on day 1 and abnormal on day 2 [34]. In contrast, in our own series of 145 Bravo studies in children, there were significantly higher values on day 1 versus day 2 for the number of long reflux episodes, duration of longest episode, and fraction of time with pH<4 in the upright position [28]. Day-to-day variability between the first and second 24-h periods may be due to the effect of anesthesia or to differences in lifestyle and dietary intake, but it is not yet clear if these differences are clinically significant. Currently, there is no consensus on how 48-h data should be interpreted in children, whether the average of 2 days or only the 24-h period with the greatest acid exposure (worst day analysis) should be used.

The Bravo wireless system appears to be a reasonable alternative to catheter-based pH monitoring for older children,

given the potential advantages in terms of patient tolerance and less effect on daily routines, diet, and activity levels. In addition, there is the potential advantage of performing an extended 48-h study to help minimize the effects of day-to-day variability. Limitations include the cost of the capsule, the need for endoscopy and anesthesia for capsule placement, as well as the risks of chest discomfort, perforation, and early capsule detachment [35, 36].

Proximal Esophageal pH Monitoring

Proximal esophageal pH monitoring is designed to assess the proximal extent of acid reflux and its relationship with oropharyngeal and respiratory symptoms. Studies employing dual-probe pH monitoring of both the distal and proximal esophagus have had mixed results however, in terms of sensitivity and specificity for extraesophageal manifestations of reflux, intra-subject reproducibility, and prediction of response to therapy [37–39]. The main limitations with proximal pH monitoring are related to the lack of consensus on the best location for probe placement and optimal pH threshold for defining a proximal reflux event. Conventionally, the same pH < 4 threshold for distal esophageal reflux has been applied to proximal measurements. There have been proposals to revise the pH criteria for proximal reflux however, based on data suggesting that nonacid reflux with pH 4–7 may also play a clinically significant role in aerodigestive disease [40, 41].

Other diagnostic modalities for the detection of proximal reflux, such as oropharyngeal pH monitoring [42–44], and the noninvasive measurement of exhaled breath condensates for the detection of proximal reflux [45, 46] have had mixed results. At the present time, the clinical advantage of proximal esophageal pH monitoring in children is not yet clearly proven, and more research is needed before these new methodologies can become part of the routine evaluation of children with extraesophageal manifestations of reflux.

Multichannel Intraluminal Impedance (MII-pH)

To overcome the limitations of pH probe, multichannel intraluminal impedance has been developed. This catheter-based system uses sensors distributed throughout the esophagus to measure resistance to flow rather than pH changes alone. The advantages to MII-pH are the following: (1) the sensors are able to determine the directionality of flow so that reflux events can be distinguished from swallows, (2) multiple sensors throughout the esophagus allows for accurate determination of refluxate height, (3) the sensors, which do not rely on pH, are able to detect nonacid reflux which is common in the pediatric and the acid-suppressed patient and in the postprandial period [47–49], and (4) because liquid and gas have different impedances, the sensors can differentiate the composition of the refluxed material.

There are seven impedance sensors placed in series which generate six impedance waves, one for each pair of adjacent sensors (Fig. 12.1a, b). Sensors are distributed throughout the esophagus at different spacing depending on the size of the catheter that is used (2–4 cm spacing on adult catheter, 2 cm spacing on the pediatric catheter, and 1 cm spacing on infant catheter). Since the impedance sensors cannot differentiate between acid versus nonacid material, a distal pH sensor has been added to the catheter which allows the clinician to determine whether the flow across the catheter is acidic, weakly acidic, or nonacidic, depending on the pH value.

The MII-pH catheter is inserted through the nose in the same fashion as traditional esophageal pH monitoring, and the catheter is positioned so the distal pH sensor is at the third vertebral body above the diaphragmatic angle (Fig. 12.2) [5]. Studies are performed for 24 h, and as with pH studies, meals are conventionally excluded from analyses. Typically, with pH studies, acid suppression medications are stopped a minimum of 48 h prior to testing because the pH probe cannot detect nonacid reflux which is prevalent in the acid-suppressed patient [50]. Since the MII-pH catheter can detect acid and nonacid reflux, the studies can be performed off or on acid suppression therapy though adult studies suggest that symptom correlation may be improved if medications are stopped prior to MII-pH testing [51].

Definitions

A liquid episode is defined as a drop in impedance to 50 % of the baseline value or below, with a subsequent recovery back to 50 % of the baseline value. This drop in impedance needs to be visualized in at least the distal two channels to be considered reflux. Gas reflux is defined as simultaneous increases in impedance to greater than 8000 Ω in two or more channels. Mixed reflux has components of both liquid and gas. By using a combined MII and pH catheter, there are mainly three types of episodes that can be detected: (a) acid reflux events detected by both the impedance and the pH sensor; (b) nonacid reflux events, which are detected only by the impedance probe; and (c) pH-only events, which are detected only by the pH sensor, without any impedance changes. In some papers, nonacid reflux is further subdivided into weakly acidic reflux (pH 4–7) and alkaline reflux (pH > 7). The importance of pH-only events is still questionable, and the current theory is that pH-only episodes represent very distal reflux that fails to reach all three distal sensors required to generate an impedance-detected episode. Studies in pediatrics suggest that these latter episodes are more common than in adults even in very young patients [52, 53].

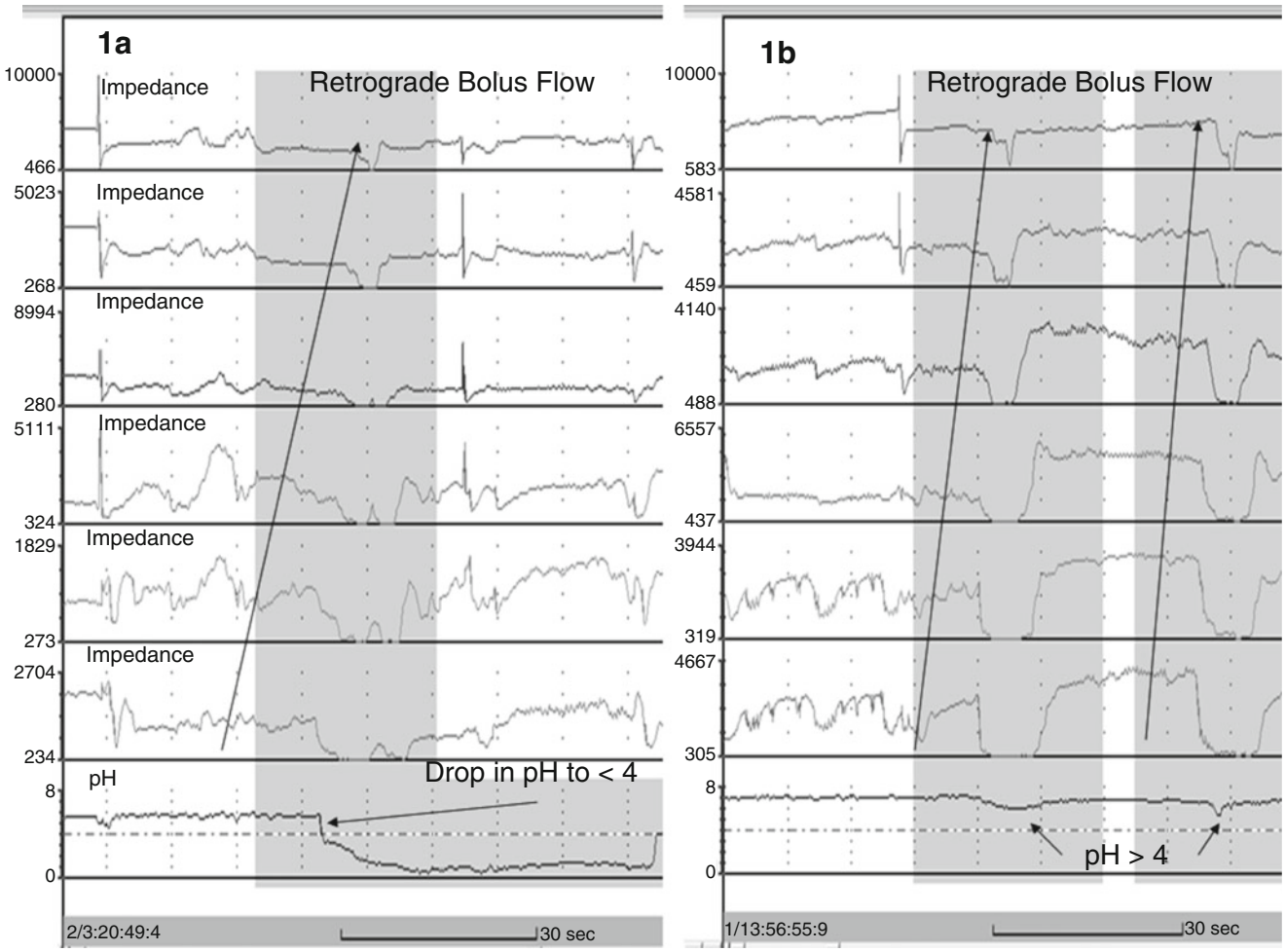

Fig. 12.1 This represents a representative impedance tracing showing an (**a**) acid and (**b**) nonacid liquid reflux event. The six upper channels are the impedance measurements (in ohms) and the lower one the pH tracing (in pH units). The arrow shows this was an episode with retrograde esophageal flow of liquid that reaches the upper most pair of sensors (full column). The pH remains above 4 at all times. Therefore, this represents a full column, nonacid liquid reflux episode. The figure also shows a clearing swallow, characterized by the antegrade progression of the impedance drops

Sensitivity

Impedance sensors have been shown to accurately detect boluses in the esophagus down to 0.1 ml^3 using fluoroscopy [54, 55]. Determining the sensitivity of MII-pH depends on the gold standard tool to which it is compared. Currently, impedance-pH monitoring is regarded as the most complete direct reflux test because it allows a full assessment of all reflux episodes, independent of their acidity [56]. Some pediatric studies have used reflux detected by any device (MII-pH and pH probe) as the gold standard. Rosen et al. found that the sensitivity of MII-pH was 76 ± 13 % compared to the pH probe whose sensitivity was 80 ± 18 %. When patients taking acid suppression were studied, the sensitivity of the pH probe dropped to 47 ± 36 %, whereas the sensitivity of MII-pH in treated patients was 80 ± 21 % [57]. Francavilla et al. found that the sensitivity of MII-pH was 86 ± 12 %, that this sensitivity was higher in infants compared to children as infants have more nonacid reflux events, and that impedance resulted in a higher symptom index, symptom sensitivity index, and symptom association probability than the pH probe [58]. Wenzl et al. found that, in untreated infants, the sensitivity of MII-pH to detect acid reflux events was 54 % compared to the pH probe [59]. Failure of MII-pH to report reflux events detected by pH probe may be due to episodes where (1) there was a persistent drop in pH less than 4 even after the bolus had been cleared by impedance, (2) the pH was hovering around 4 with multiple drops to less than 4, or (3) there were pH drops associated with swallows.

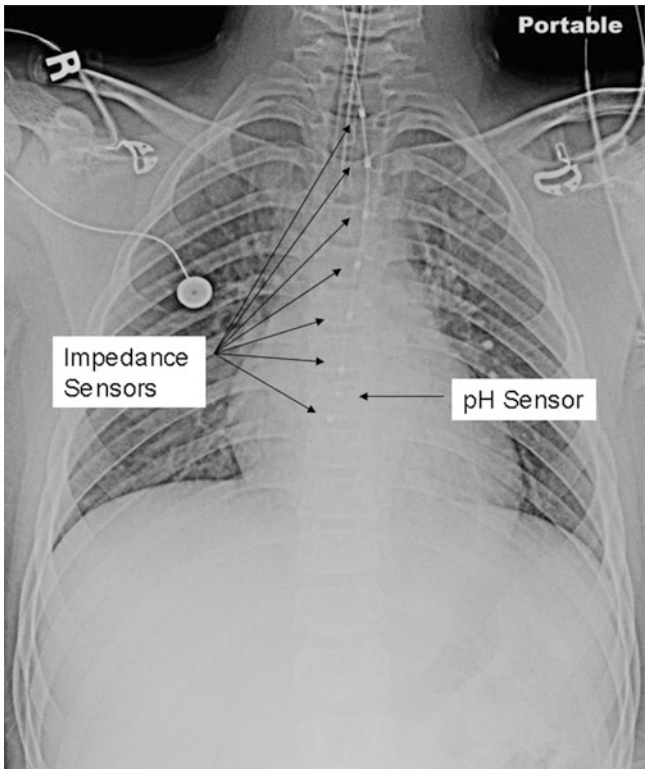

Fig. 12.2 Chest X-ray showing placement of an impedance catheter. The longitudinal array of the impedance sensor can be observed. The catheter is positioned such that pH electrode is at the third vertebral body above the diaphragmatic angle

Reproducibility

Dalby et al. performed 48-h impedance studies in 30 children to determine the degree of variability between the first and second day of recording [60]; the authors found that the reproducibility of the total number of reflux events with each patient between days was better than the reproducibility of the number of acid or nonacid events individually. On a population basis, there was no significant difference between the median total number, acid, or nonacid events between days 1 and 2 [60]. Aanen et al., in a study of 21 adults, found that the number of acid, weakly acidic, and total events was similar between the 2 days with a Kendall's W value of 0.9, 0.9, and 0.92. Additionally, the reproducibility of the symptom indices using the SAP, SI, and SSI was 0.9, 0.73, and 0.86, respectively [61]. Similarly, Zerbib et al. found, in 27 adults, that there was good reproducibility for the number, acidity, and composition of reflux events (Kendall's W values = 0.72–0.85) [62].

Interpretation

The interpretation of impedance tracings is time-consuming and, in most research laboratories, is still done manually even though there is commercially available analysis software based on well-defined impedance criteria. Roman et al. studied the reproducibility of the automated software (Sandhill Scientific) to detect reflux events compared to manual scoring of the events and found that automatic analysis overestimated the number of nonacid reflux events [63]. Hemmink et al. also compared automated software analysis (Medical Measurement Systems) to manual scoring and found that the sensitivity of the software was 73 ± 4 %. Additionally, the automated software incorrectly determined a symptom association 16–20 % of the time, depending on the symptom index used [64]. There are select populations where automated analysis may be particularly inaccurate; manual interpretation is critical if there is esophagitis present or if there is a motility disorder such as achalasia or esophageal atresia all of which lowers impedance baselines. This low impedance baseline result is significant in underestimations of the amount of reflux present.

Although most investigators prefer manual analysis of MII-pH tracings to ensure confidence in marking of GER episodes, there is also concern regarding the potential for interobserver and intraobserver variability. In Loots et al., comparison of manual analysis of ten MII-pH tracings by ten experts from around the world yielded only moderate agreement (Cohen's kappa [k] = 0.46), with only 42 % of all reflux episodes being identified by the majority (≥6) of observers [65]. Therefore, while manual analysis may be more accurate than automatic analysis for detection of individual reflux events, interobserver variability may limit the ability to compare results between different centers.

Normal Values

One of the current limitations to MII-pH monitoring is the lack of normal pediatric values to differentiate physiologic from pathologic reflux. Adult normal values have been published: Shay et al. conducted a multicenter study of 60 healthy volunteers and found that the upper limit of normal for total, acid, weakly acid, and nonacid reflux were 73, 55, 26, and 1, respectively [66]. Zerbib et al. found similar numbers in normal adults with the upper limit of normal for healthy adults for total, acid, weakly acid, and nonacid reflux were 75, 50, 33, and 15, respectively [62].

Normal preterm infant values differ significantly from adults; the upper limit for total number of reflux events is 100 of which up to 52 % can be acid and up to 98 % can be nonacid; however, these values were obtained with an nasogastric tube in place which can falsely increase the amount of reflux by stenting open the lower esophageal sphincter [47]. In contrast, in a small study of older children ($n = 10$, patients with normal pH recording and normal esophageal biopsies and no gastrointestinal symptoms), the 95th percentile for total events was 69 which is very similar to adult data [67]. A subsequent larger study in children, consisting of 46

infants and 71 children referred for reflux testing, but found to have normal pH index and negative symptom correlation, reported similar results: the 95th percentile for total GER events in infants was 93, while in children it was 71 [68]. Although these cutoff values appear to be relatively consistent, none of these studies contained true "normal" patients as they were all symptomatic and thus referred for impedance testing. Because normative data derived from healthy, asymptomatic volunteers are not available in pediatrics, the main role of impedance at this time should be to correlate symptoms with reflux events.

Symptom Association

Given the lack of normative data to determine normal MII-pH in children, the most important use of the technique has been to study the temporal association between symptoms and reflux. There is significant debate in the adult literature about the optimal way to correlate reflux with symptoms, but the literature is clear that MII-pH is superior to pH probe alone when looking for symptom correlation [40, 51, 69, 70]. The rates of symptom index (SI), symptom sensitivity index (SSI), and symptom association probability (SAP) positivity have been studied using MII-pH. In the adult literature, the SAP and the SSI were most reproducible indices in patients that had two impedance studies separated by a minimum of 1 week. Similarly, Brendenoord et al. found that the SAP was the most frequently positive index followed by the SI and then the SSI. They also found that the addition of MII-pH over a standard pH probe increased the number of patients with a positive SI and SAP but did not increase the number of patients with a positive SSI [69].

Rosen et al similarly studied 28 children taking acid suppression therapy for intractable respiratory symptoms; in these patients, more patients had a positive SI for respiratory symptoms using MII-pH than pH probe alone, but there was no difference in the number of patients with a positive SSI when MII-pH was used compared to a standard pH probe [40]. In contrast, Thilmany et al. found that the rate of positivity for the SI was higher for acid reflux episodes, whereas the rate of positivity of SSI was higher for nonacid reflux episodes suggesting that the value of MII-pH may differ depending on what symptom index is used [71]. Loots et al. studied 50 children undergoing MII-pH testing and found that uniformly, MII-pH resulted in a higher symptom association, regardless of the index used, compared to pH probe and that the SAP was the most frequently positive symptom index [72].

One of the limitations of symptom indices is that they only represent a significant temporal relationship rather than a true cause and effect relationship. The cutoff values, therefore, represent statistical definitions and are not necessarily tied to clinical outcomes. For example, if a patient has a symptom index greater than 50 %, one would expect, if this means reflux is causing symptoms, that the patient will have a favorable outcome to acid suppression therapy or, more definitively, to fundoplication. Unfortunately, the normal values of 50 % for the SI, 10 % for the SSI, and 95 % for the SAP were not generated by looking at clinical outcomes. In adults, patients with a positive SAP have been shown to be more likely to have symptomatic response to both medical and surgical anti-reflux therapy [73]. On the other hand, Rosen et al. looked at the value of the SI and the SSI in predicting fundoplication outcome; they found that neither a positive SI nor SSI predicted fundoplication outcome, and using ROC curves, there was no clear cutoff value for either index which predicted fundoplication outcome [74]. This data suggests that a temporal association alone does not prove causality which is the key limitation to all of the symptom indices.

A second limitation of the symptom indices is the time lag between when a symptom occurs and when the patient actually records the symptom. In a study by Sifrim et al., there was an average delay of 28 s between the time when a patient coughed and when they actually recorded a cough on the symptom log [75]. Furthermore, patients only record, on average, 38 % of coughs on the log [75]. To address this limitation, impedance sensors can be paired with pressure sensors, the latter of which measures esophageal pressure spikes that occur when a patient coughs. Coughs appear as simultaneous high-pressure spikes in the esophagus (Fig. 12.3), and this allows for precise correlation between reflux and cough without the possibility for recording error. In a study of 20 children undergoing intraesophageal pressure recording with pH-MII testing, Rosen et al. found that only 48 % of all coughs during reflux testing were reported by patients and there was a delay of 11 ± 16 s between the actual cough and patients reporting the cough [76]. Because the placement of two catheters can be uncomfortable, use of intraesophageal pressure recording may be limited in children. More recently, Rosen et al. showed that noninvasive acoustic cough recording, which entails the taping of microphones over the trachea and chest wall, to be equally sensitive as intraesophageal pressure recording to detect cough in children, and this technology increased the detection of cough by more than 100 % over patient report alone [77].

Thirdly, a clear definition of the optimal time interval is lacking. By consensus, a time interval of ±2 min is generally used, but other time intervals have also been proposed depending on the symptoms of interest. Finally, an effective method to evaluate the symptom-reflux association in long-lived symptoms such as wheezing or sore throat has not been defined.

Extraesophageal Reflux

Extraesophageal manifestations of GERD (chronic cough, asthma, and laryngitis) continue to pose a diagnostic and therapeutic challenge for gastroenterologists. Rightly or not,

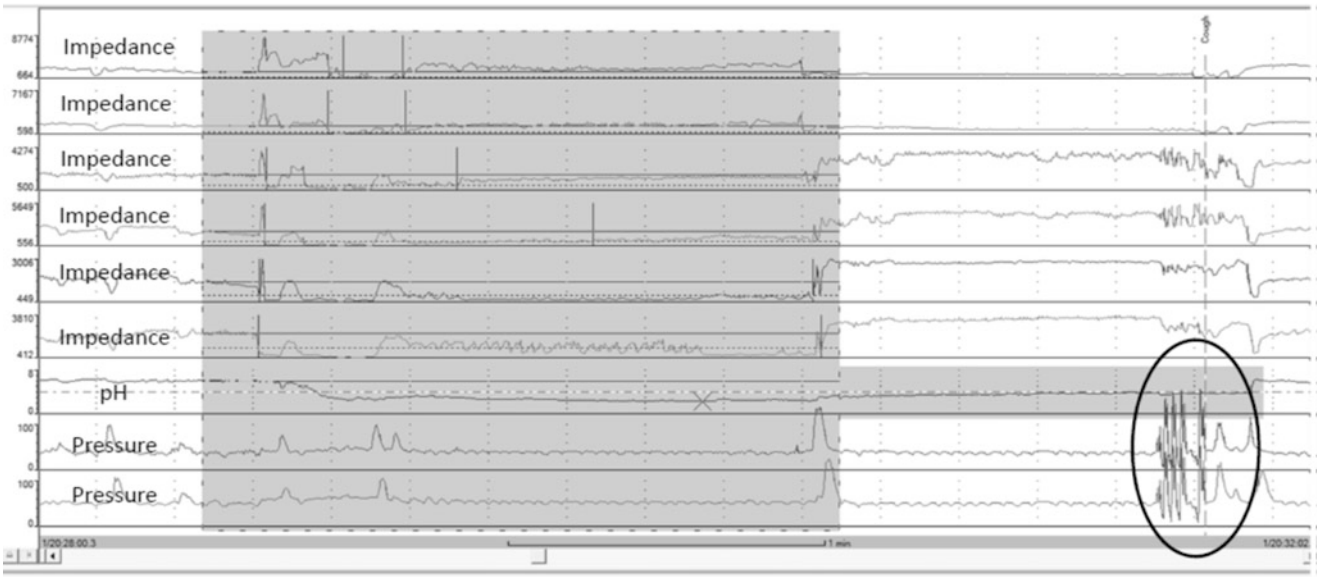

Fig. 12.3 Impedance tracing that shows the association between reflux and cough with the use of a cough catheter which detects simultaneous increase in intrathoracic pressure. The six upper channels are the impedance measurements (in ohms) and the lower one the pH tracing (in pH units). There are also two distal pressure channels which capture coughs and peristalsis. This tracing shows an acid reflux event that precedes a cough burst (*circle*)

these chronic symptoms are often attributed to GERD without concomitant typical GERD symptoms of heartburn and regurgitation. One of the advantages of MII-pH is that the multiple sensors can detect full column reflux which is extremely important when determining the impact of reflux on the airway and beyond. Rosen et al. found that, in children with intractable respiratory symptom, full column reflux is more highly associated with respiratory symptoms than distal reflux [40]. The importance of full column reflux in the generation of symptoms is further supported by Jadcherla et al. who found that acid reflux events reaching the proximal esophagus were four times more likely to be associated with symptoms than distal events [78]. The next step is to determine whether full column reflux predicts clinical outcome. Rosen et al. found that full column reflux events, rather than total reflux burden, predicted a positive surgical outcome [74]. In other studies, the relationship between full column reflux and symptoms is less clear. In a study of 40 adult subjects, there was no difference in the percentage of symptom-related reflux with proximal extension between typical esophageal symptoms and extraesophageal symptoms such as cough and throat clearing [39]. Condino et al. found that, in asthmatic children, proximal reflux was not a predictor of symptom generation [70]. Because extraesophageal symptoms are a heterogeneous grouping of diseases, it is often difficult to determine a definitive relationship between full column events and symptoms.

Novel Impedance Parameters

Determination of baseline impedance (BI), which measures the resting impedance of the esophageal mucosa in the absence of swallowing or reflux events, is a novel impedance parameter and has been proposed as a potential biomarker of mucosal integrity. Work by Farre et al. first showed the correlation between BI and mucosal integrity based on in vitro and in vivo studies of acid perfusion in animals and humans [79]. Low BI has subsequently been shown to correlate with increased acid reflux parameters as well as histopathologic findings of GERD [80]. Furthermore, treatment with proton pump inhibitor therapy has been associated with significant increases in BI measurements in both adult and pediatric subjects [81, 82]. Despite the encouraging data for BI as a GERD biomarker, there is no uniform agreement on how, where, or when to measure BI in the 24-h tracing, nor is there consensus on normative cutoff values for diagnosis or prediction of response to therapy. Finally, it is not clear that baseline impedance values add any additional, clinically relevant data above standard impedance measurements [83].

Another novel use for impedance is the pairing of impedance sensors with high-resolution esophageal manometry. This pairing allows the clinicians to determine the relationship between peristaltic abnormalities and bolus movement; this pairing is critical as studies suggest that bolus clearance can be normal in the majority of swallows in patients diagnosed

with motility disorders raising into question the significance of these motility diagnoses [84]. The addition of impedance to HRM also facilitates the diagnosis of rumination syndrome when retrograde bolus movement is seen presence of R waves in the stomach and esophagus [85].

Role of Assessing Therapy

One of the most helpful uses of MII-pH is to objectively determine the efficacy of both pharmacologic and non-pharmacologic reflux therapies. Impedance has been used to study the effect of different noninvasive therapies in children. Wenzl et al. used MII-pH to study 14 infants who received thickened and thin feeds in an alternating fashion. The authors found that the amount of formula that was regurgitated out of the mouth was reduced with thickened feeds but that the number of reflux events and the height of the reflux events were not statistically different between the two groups [86]. Similarly, Corvaglia et al. studied, using MII-pH, five preterm infants who received alternating thin mother's breast milk (MBM) and MBM thickened with starch and found that thickened feeds did not reduce the amount of total, acid, or nonacid reflux [87].

Several studies in infants have been performed to determine the impact of positioning on reflux [88–90]. Omari et al. studied preterm infants in the right and left lateral decubitus positions and found that, in the postprandial period, there is significantly more reflux in the right lateral decubitus position and that the primary mechanism for this increase in reflux is an increase in the numbers of transient lower esophageal sphincter relaxations [90].

Another advantage of impedance is that it allows for the measurement of nonacid reflux which is higher in the postprandial period. Therefore, MII-pH is an ideal tool to measure the effects of different methods of feeding on reflux. Peter et al., for example, fed preterm infants with and without an NG tube traversing the lower esophageal sphincter and found that there was a significant increase in the amount of reflux with an NG tube in place [91]. Rosen et al. studied the rates of reflux during transpyloric feeds and found that rates of reflux were lower in patients that were fed transpylorically compared to children with GERD but that reflux still occurred in children with transpyloric feeds and the rate of reflux during feed periods was double that of non-feed periods [92]; the significance of this persistent reflux depends on the patient, but rates of hospitalization for respiratory disease are reduced after the initiation of transpyloric feeds and rates of hospitalization reduction are comparable to fundoplication [92, 93].

MII-pH serves an important role in the determination of reflux medication efficacy. In a study by Vela et al., MII-pH studies were performed before and during a trial of omeprazole; the authors found that omeprazole converted acid reflux to nonacid reflux but did not change the total number of reflux episodes [50]; this was a critical finding because it explained why some patients continue to experience symptoms despite acid suppression therapy. In a study by Loots et al., left-sided positioning and antacid use reduced vomiting episodes, while PPI use reduced acid reflux burden in these infants [94].

MII-pH has also been used to assess the efficacy of motility medication. One class of medications that have been evaluated using MII-pH are the GABA agonists (baclofen, arbaclofen, lesogaberan) which uniformly reduce both acid and nonacid reflux burden, but none have been approved for use in pediatric reflux [95–97]. More recently, a study using MII-pH to assess the efficacy of azithromycin, a motilin agonist, found that acid reflux but not total reflux episodes were reduced after the administration of the drug [98]. Finally, in a study of 13 infants receiving domperidone, a dopamine antagonist with promotility properties, there was actually an increase in reflux events after administration of the medication, disproving its utility in infants with reflux [99].

Finally, MII-pH has been used as a tool to predict clinical response to fundoplication. Adult studies have found that MII-pH may predict which patients respond symptomatically to fundoplication [100, 101], but pediatric studies are limited and are less encouraging that the amount of reflux predicts surgical outcome [74]. More recently, adult studies have suggested the post-fundoplication MII-pH studies may predict who responds to reoperation, but again there is no pediatric data to confirm this [102].

Impedance and Clinical Outcome

While MII-pH has clearly become critical to determine, from a research perspective, the role of impedance in improving clinical outcomes is uncertain at this time. Several adult studies have shown that MII-pH may predict a clinical response to therapy including proton-pump inhibitors [73, 100, 103]. There are several pediatric studies to address the role of MII-pH testing in predicting outcome. Rosen et al. gave the results of the pH portion of the test and asked the ordering gastroenterologist how the pH results change management. The MII portion of the test was then given to the ordering clinician who was again asked how this result changed clinical management. Out of 50 impedances ordered by 23 gastroenterologists, the MII portion of the test changed the clinical management of the patient 22 % of the time. In a study of children undergoing pH-MII testing prior to fundoplication, the results of pH-MII testing suggest that no reflux parameter other than the amount of full column reflux could

predict symptom resolution after fundoplication [74]. Finally, in a recent study of 116 children undergoing impedance, abnormal reflux parameters by pH-MII did not predict hospitalization risk even in high-risk patients with aspiration [104]. Additional prospective studies are needed to determine how MII-pH impacts patient outcomes.

Future of Multichannel Intraluminal Impedance

Currently, based on the evidence, MII-pH has replaced the gold standard pH probe for the evaluation of reflux in a research setting. Because of its ability to detect full column reflux and acid and nonacid reflux, it is ideal for patients with persistent symptoms on acid suppression, for patients with symptoms in the postprandial period, for patients with extraesophageal symptoms, and for patients continuously fed into the stomach. Perhaps the most powerful indication is its pairing with manometry to assess esophageal function. However, clearly outcome studies are needed to prove its utility in clinical practice.

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Barostat and Other Sensitivity Tests

13

Christophe Faure

Visceral sensitivity is a complex phenomenon that is regarded as a key pathophysiological factor in children with FGID. In the recent years, techniques have been developed in adults and adapted to children making possible measures of visceral sensory thresholds of stomach and colon. This chapter reviews the barostat technique and the satiety drinking tests. Functional cerebral imaging and other chemical stimulations that have not been extensively applied in pediatric subjects will not be discussed.

Barostat

Principles

The barostat is a computer-driven air pump connected to a double-lumen catheter on which a highly compliant balloon or bag is securely fixed. The balloon is introduced in a hollow organ (in children rectum or stomach) and is used to measure tone, compliance, and sensory threshold (Fig. 13.1). The principle of the barostat is to maintain a constant pressure within the air-filled bag inserted in the organ: when the organ relaxes, the air pump inflates the balloon to maintain a constant pressure; when the organ contracts, the system withdraws air and deflates the balloon. Because in barostat studies, the function of the bag is to isolate a segment of the digestive tract without interfering with its function and its motility, the compliance of the balloon or bag should be "infinite," and the volume must be greater than the range of volume used during the study (rectal bags, length 11 cm, maximal capacity 600 mL; gastric bags, maximal diameter 17 cm, maximal capacity 1200 mL). Polyethylene bags are recommended versus latex balloons.

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Because visceral sensitivity relies on wall pressure and not on volume of the organ [1, 2], sensory thresholds should be expressed as pressure. Moreover, reproducibility of pressure measurements between laboratories and between subjects is better than volumes because the pressure scale compensates for differences in bag shape, smooth muscle compliance, and contractile activity of the organs [3].

Procedure

Technical recommendations for measurements of sensory threshold and compliance have been published in adults, and the general principles apply to practice in children [3]. However, sensory threshold assessment requires an adequate cooperation for the report of the sensations and feelings by the subject. Children younger than 7–8 years may not be able to relate adequately their sensations during the procedure. Explanation on equipment and sequence of the procedure must be given to the child and the parents. Because psychological state modulation results in changed sensation at a given stimulus in healthy adult subjects [4], environment and sequence of the barostat study should be as quiet as possible in order to minimize the external influences and standardize the procedure.

For rectal sensitivity studies in children, most authors do not clean extensively the colon but rather suggest to the child to go to the bathroom before the study. For study compliance in children with constipation, cleansing of the rectum with enema should be conducted the day before the barostat study. Because meal may interfere with colonic and gastric tone, a 4–6-h fasting period prior to the study is recommended. All medications affecting pain or gastrointestinal motility should be discontinued at least 48 h prior to the barostat procedure.

For rectal studies, the patient lies in the left lateral position and the catheter is gently inserted into the rectum. For gastric studies, the catheter is inserted by mouth. The catheter is secured with a tape and 5–10 min is allowed for adaptation before beginning the procedure. The barostat bag is then

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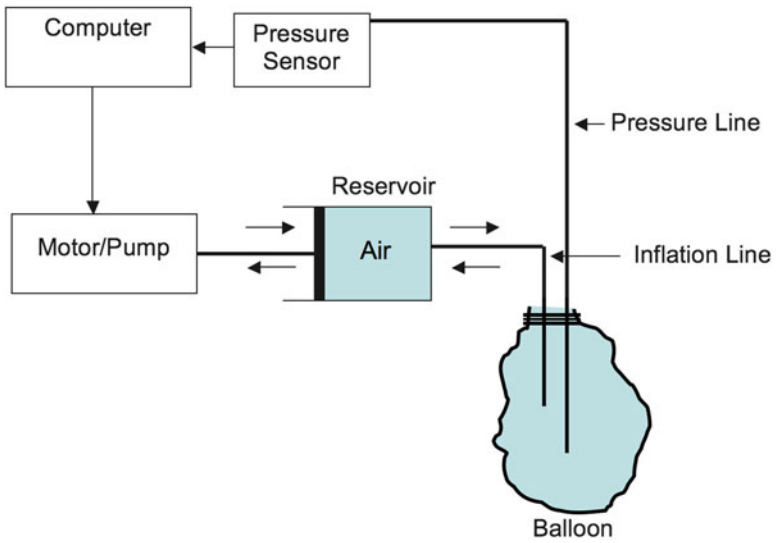

Fig. 13.1 Schematic diagram of a barostat and catheter

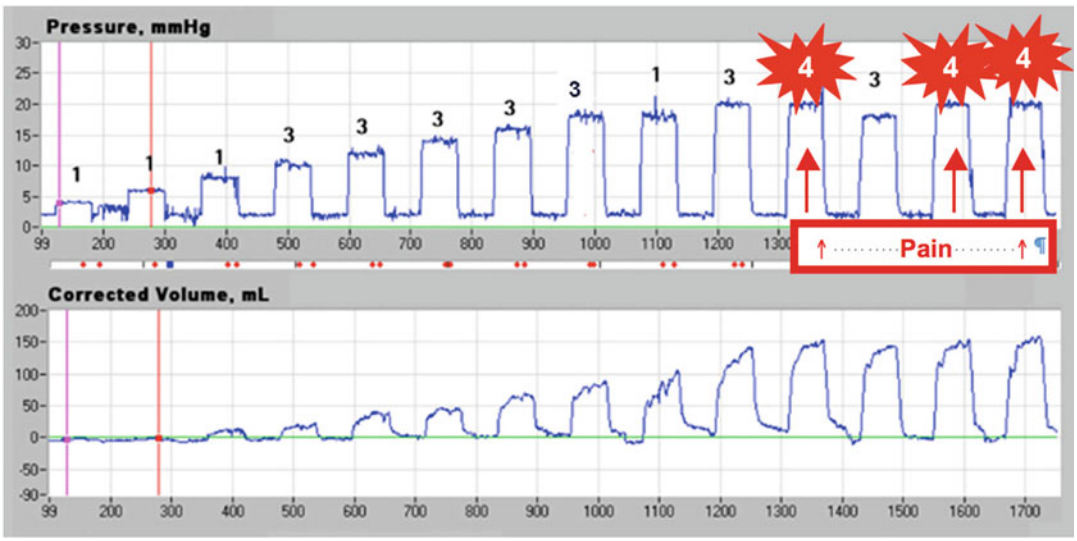

Fig. 13.2 Ascending method of limits with tracking. Rectal barostat tracing in an 11-year-old girl with irritable bowel syndrome (IBS). Verbal scale: (*1*) gas or first sensation, (*2*) need to go to the bathroom, (*3*) urge to go to the bathroom, (*4*) pain

slowly inflated with 30 mL of air and the pressure is allowed to equilibrate for 3 min. The average bag pressure during the last 15 s defines the individual operating pressure (IOP) also called the minimal distending pressure (MDP) which is the minimum pressure required to overcome mechanical forces and inflate the bag with 30 mL of air.

Various distension protocols have been described [3]. In children, the ascending method of limits (AML) without [5–7] or with [8–13] tracking has been the most applied. In the AML, the barostat is programmed to deliver phasic intermittent stimuli starting at the IOP progressively increased in 2–4 mmHg steps lasting 60 s followed by 60 s deflation. When the first sensation of pain is reported, the study can be stopped (the sensory threshold is determined) or can be prolonged (tracking) by subsequent distensions randomly adjusted up or down depending on the response of the previous distension (if the subject reports pain, the next distension will be decreased or kept the same; if the subject reports no pain, the next distension will be increased or kept the same). The threshold is determined by averaging the pressures at which pain had been indicated after a series of measures (usually three) (Fig. 13.2). A four- to five-point scale [6, 10] is used as a verbal descriptor for sensation felt during the barostat procedure. The AML is vulnerable to psychological biases (fear of pain) because the stimuli are predictable to the subject. The tracking technique is believed to be more

reliable because it is less vulnerable to psychological bias (the stimuli is unpredictable) and because there are multiple determinations of the threshold. On the other hand, the tracking technique necessitates delivering multiple painful stimuli that can be less acceptable in children. However, the tracking method has been used successfully without any adverse event by several pediatric groups [8–13]. Of note the majority of children tested report that the pain sensation felt during the barostat is notably lower than the pain felt in the *real life*.

Measurements

Sensory Thresholds

The visceral sensory threshold can be separated into two components: the *perceptual sensitivity* (the ability to detect intraluminal distension) and the *response bias* (how the sensation is reported). The perceptual sensitivity allows to discriminate between two distensions and reflects the ability of the organ to detect and transduce the stimulus to the central nervous system. The response bias (or perceptual response) is the reporting behavior (intensity, painfulness) that is a cognitive process influenced by past experience and psychological state. Actually, the tools currently used (distending protocols, methods for reporting subjects' response) are not able to accurately measure separately the two components. Adult studies have shown that the threshold measurement is responsive to changing environments or perturbations and psychological modulation results in changed sensation at a given stimulus in healthy subjects [4]. In children, there are few data regarding the influence of psychological state or trait on sensory threshold assessment. One pediatric study found that rectal sensory threshold did not correlate with the *state* of anxiety, suggesting that the anxiety generated by the procedure itself is not sufficient to bias the child's response to distension [10]. However, visceral sensitivity study should be conducted in a neutral and quiet environment in order to avoid any external interference with the measurements. Results can be expressed as sensory thresholds, i.e., the first pressure that triggers a given sensation (urge to defecate, pain), or in intensity of sensation triggered by stimuli at fixed pressure.

Compliance

The compliance reflects the ability of a hollow organ to adapt to an imposed distension. It is expressed in mL/mmHg. It is defined as the pressure-volume relationship which sigmoid shape is composed of an initial reflex relaxation followed by a linear section and a final plateau phase. Practically, compliance is calculated according to a nonlinear model fitting the pressure-volume curves. Pressure-volume curves are constructed with average computed volumes during each consecutive pressure step (when equilibration of the volume is reached, typically after 30–45 s). Compliance is calculated as the maximum slope of the pressure-volume curves (Fig. 13.3) [3, 9, 12, 14–18]. Normal pediatric values have been published for rectal compliance (22 healthy volunteers 12 ± 2.6 years, 16 mL/mmHg, 12–20 [16]; ten control children mean age 13.7 years, 8.7 mL/mmHg, 6.0–14 [12]). Alteration of gastric compliance has been reported in eight children after Nissen fundoplication [17, 19–21].

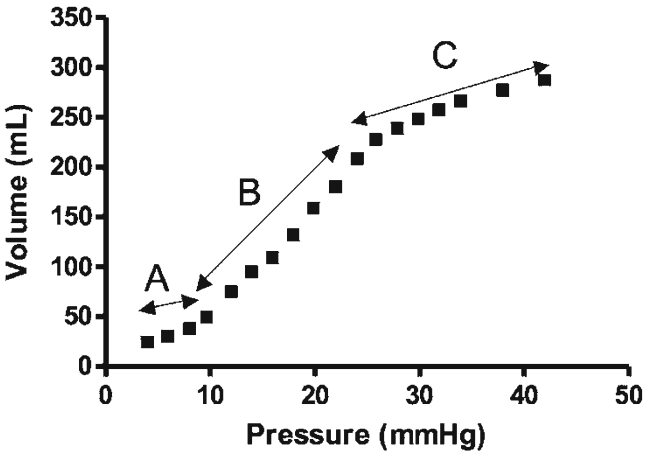

Fig. 13.3 Normal relationship volume-pressure (compliance = 9.1 mL/mmHg) in the rectum of a 12-year-old IBS patient. The sigmoid curve is composed of an initial reflex relaxation (*A*) followed by a linear section (*B*) and a final plateau phase (*C*). Compliance is calculated as the maximum slope of the curve in the linear section (*B*)

Tone and Accommodation

The volume of air entering or withdrawn from the balloon is an indirect measurement of tone of the organ. Changes in volume in response to a meal (accommodation) can thus be easily measured by subtracting preprandial to postprandial balloon volumes. Rectal volume response to feeding (decrease of 25 ± 3 % from 88 ± 8 mL before the meal to 66 ± 7 mL after the meal) has been reported in healthy children [6]. In the stomach, no data have been reported in children but in young adults [18].

Qualitative and Quantitative Assessment of the Sensations

Sensations elicited during the barostat, painful or not, must be rated (intensity) and qualitatively reported. Visual analog scale can be used by children aged 6–7 years to rate sensations such as urgency or pain [9, 11, 12] and is easier to use than verbal descriptors in this population. Rating separately pain from unpleasantness is difficult in children. Qualitative evaluation of the pain has been conducted by using validated human body diagrams [10, 22] and questionnaire related to the similarity of the induced pain and the typical pain felt in the real life [9, 13].

Clinical Relevance of Barostat Measurements

Pain-Associated Functional Gastrointestinal Disorders

Rectal Sensitivity Measurement

Using rectal barostat, several independent groups have reported that 75–100 % of children with IBS have rectal hypersensitivity as compared to control children [6, 8–10, 13]. In adults affected by IBS, the prevalence of visceral hypersensitivity varies from 20 % [23] to 94 % [24] across studies suggesting that rectal hypersensitivity is a more reliable diagnostic marker of IBS in children than in adults. This has been confirmed in a prospective study that included children with abdominal pain for whom rectal sensory threshold was measured prior to any other diagnostic procedures [9]. In the 51 children included, rectal sensory threshold was lower in the FGID group than in the organic disease group (25.4 mmHg vs. 37.1 mmHg; $P=0.0002$), and 77 % of the children with FGID had a rectal hypersensitivity. At the cut-off of 30 mmHg, the RSTP measurement for the diagnosis of FGID had a sensitivity of 94 % and a specificity of 77 %. Rectal compliance has not been found different in IBS and control subjects [6, 8, 9, 11, 13]. Children with functional dyspepsia have normal rectal sensitivity suggesting that visceral hypersensitivity is organ specific [10].

Data regarding visceral sensitivity in children with functional abdominal pain (FAP) according to Rome criteria are less clear with discrepancies (sensory threshold similar to controls [6] or similar to IBS [10]) between authors.

Gastric Sensitivity Measurement

Because of the invasiveness of gastric barostat, the pathophysiology of functional dyspepsia (FD) has been scarcely studied in children. A subset of children with recurrent abdominal pain studied by gastric barostat using a latex balloon were reported to present hypersensitivity at the gastric level [13]. More recently, 16 dyspeptic children were extensively studied using gastric barostat [18]. Compliance was similar between patients and controls (69.5 ± 8.9 mL/mmHg). Pressures at the discomfort threshold were significantly lower in dyspeptic children compared with young healthy controls. Accommodation to a meal was significantly lower in dyspeptic children. Hypersensitivity to gastric distension was present in 56 % (9/16) of patients and impaired accommodation in 11 patients (69 %). When studied by gastric barostat, children with IBS have normal gastric sensitivity [13].

Somatic Projections and Reproducibility of the Visceral Pain

Somatic referral induced by rectal distension differs in IBS, FAP, and FD children. In normal children without any gastrointestinal complaints and in dyspeptic patients, rectal distension-induced sensations refer to the S3 dermatome (perineal area). In IBS and FAP, children refer their sensation to aberrant sites compared to the controls, i.e., with abdominal projections to dermatomes T8 to L1 [10]. However, similar results have been obtained in barostat study of children with organic diseases suggesting that subjects with protracted complaints of abdominal pain not related to FGID may have in contrast to "true" controls an abnormal perceptual response to distension (i.e., abnormal interpretation and sensation in response to rectal distension) [9]. The reproduction of pain during rectal distension is frequent in IBS and FAP children but is not predictive of a diagnosis of FGID as compared to organic diseases [9].

Constipation

In constipated children, a high rectal compliance (>20 mL/mmHg) is present in a majority (58 %) of patients and explains that, to reach the intrarectal pressure threshold that triggers the sensation of need to defecate, a larger stool volume is required. Actually in contrast to previous studies, only 10 % of the patients have a true rectal hyposensitivity [15, 16]. Whether the abnormal rectal compliance is primitive or secondary to fecal impaction is uncertain although there is no difference in compliance between groups with and without impaction [16]. Moreover, rectal emptying by regularly using enemas does not normalize compliance [15].

Less Invasive Methods to Assess Gastric Sensitivity

Because gastric barostat studies are more invasive than rectal barostat, less invasive methods of measure of gastric sensitivity have been developed.

Water Load Test

The water load test has been advocated as a means of identifying patients with gastric hyperalgesia. The water load test can be performed according to two different techniques. The first involves the patient drinking water at a fixed rate (e.g., 100 mL/min) until he or she reports being "full." The second method, which has been used in pediatrics, is referred to as rapid water loading and involves the patient drinking water ad libitum over a 3–5-min period [25]. Practically, the child must drink from a glass as much water as possible poured from a liter bottle in 3 min or until he/she feels too full to continue [25, 26]. In a non-controlled small study, the maximum water intake capacity was found reduced in children

with functional dyspepsia ($n=11$, median = 380 mL) as compared to patients with irritable bowel syndrome ($n=10$, median = 695 mL) or functional abdominal pain ($n=10$, median = 670 mL) [27]. However, the water load test seems to be a poor diagnostic test for functional dyspepsia because of poor sensitivity [26]. Interestingly, the water load test was used to demonstrate that obese children and adolescents have to drink 20 % more water until the onset of satiety when compared with normal-weight participants [28].

Satiety Drinking Tests

Satiety drinking test with a liquid meal has been validated in adults and is correlated to gastric barostat measurements [29]. Subjects are studied after an overnight fast. A peristaltic pump fills one of two beakers at a rate of 15 mL/min with a liquid meal (Nutridrink [30], Ensure [31]). The children are instructed to maintain intake at the filling rate, thereby alternating the beakers by filling and emptying. For every 5 min, they score their satiety using a graphic rating scale, graded 0–5 (1 = no sensation, 5 = maximum sensation). Satiety is defined and explained to the children as the opposite of desire to eat. Children are asked to cease the meal intake when a score of five is reached. The maximal tolerated volume reflects gastric accommodation. This method has been used in a large group of 59 children aged 5–15 years for which normal values have been published [30]. Adolescents with FD have been shown to present increased symptoms 30 min after reaching maximum satiation [31].

Intragastric Pressure During Food Intake

Recently, using a standard catheter for high-resolution esophageal manometry, the intragastric pressure during nutrient drink ingestion has been validated versus gastric barostat as a minimally invasive technique for assessment of gastric accommodation. Upon nutrient drink ingestion, intragastric pressure drops initially and gradually recovers [32]. This technique has been applied in children with functional dyspepsia [33].

Functional Lumen Imaging Probe

Functional lumen imaging probe (FLIP) is a new technique allowing the assessment of distensibility and compliance of hollow organs and sphincters [19, 20]. The currently available equipment is suitable for esophagus [21] and anal sphincter [20]. Data in children are currently lacking.

Role of Visceral Sensitivity Measurement in Clinical Practice

By providing an objective criterion in addition to the clinical symptoms of FGID, the determination of a low sensory threshold may give a pathophysiological explanation to children and their parents, making it possible for them to understand the nature and mechanisms of the symptoms. This may be helpful to reassure patients, their parents, and physicians by confirming the clinical symptom-based diagnosis of FGID. On the other hand, children with IBS or FAP symptoms with a normal RSTP should be carefully reexamined to exclude other diagnoses. Rectal hypersensitivity has been reported in children with inactive Crohn's disease suffering from protracted abdominal pain suggesting that rectal barostat may be useful to recognize FGID in such patients [12]. Whether measurement of visceral sensitivity impacts the outcome of patients with FGID (number of procedures ordered by the physician, long-term prognosis, and response to drugs) is unknown. Less or noninvasive means to assess visceral sensitivity are important to be validated in pediatrics to allow an easier and larger determination of this physiological parameter to further understand and treat FGID. The lactulose challenge test which allows to discriminate patients with IBS and which is correlated with rectal barostat measurements is as such a promising tool [34].

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Radionuclide Gastrointestinal Transit Tests

14

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Scintigraphic techniques in the investigation of the gastrointestinal tract (GIT) have been in clinical use for decades but until recently have been little utilized in clinical practice [1, 2]. Scintigraphy is considered the gold standard for measuring gastric motility, but its clinical application has been limited in view of the lack of standardization of the technique. The large variety of the radiolabeled meals in use has made it difficult to define a normal range that is applicable to all centers, thus generating uncertainties in the value of the technique. The difficulty in recruiting pediatric normal volunteers to establish a normal range of the radionuclide gastric emptying study has added to the problem. Small bowel and colonic transit scintigraphic studies in children are performed only in selected specialized centers.

The major change over the last 10 years is the publication of a new set of guidelines that clearly define the radiolabeled meal to be used for a radionuclide gastric emptying study [3, 4]. The guidelines also define the normal range in adults for a solid gastric emptying meal based on radiolabeled egg white. This publication is a milestone; as a result of it, many centers around the world have started to adopt the newly defined standard radiolabeled meal and the relevant acquisition protocol, with significant improvement in the accuracy and reproducibility of the results.

New guidelines on the acquisition of the whole-gut transit study, including the stomach, small bowel, and colon, have also been published more recently [5]. It is hoped that the small bowel and the colonic transit studies will also gain more acceptability in clinical practice, as a result of many centers implementing the proposed recommendations.

Pediatric nuclear medicine traditionally lags behind adult nuclear medicine practice because of a smaller patient population and fewer specialized pediatric centers around the world. In addition, some aspects of pediatric nuclear medicine are unique due to differences in organ size, patient's cooperation, and neurological and developmental maturation. We are still a long way off pediatric GI transit studies becoming accepted as a part of routine clinical investigation. The main issues that require validation are the normal range in different pediatric age groups, a standardized acquisition protocol for each study, and an alternative radiolabeled meal to be used in the case of intolerance to the standard meal based on eggs. However, work is in progress in several specialist centers around the world to address these issues.

Scintigraphic tests are attractive as a means of providing exquisite gastrointestinal function under physiological conditions, with a set of low-cost procedures that are easy to perform, well tolerated, and not operator dependent [6]. The radiation burden is smaller than conventional radiology, and as γ-cameras are linked to digital computers, quantification is relatively easy. Performing scintigraphy in children requires great patience and skills from the radiographers and technicians who interact with the child and family at the time of the examination. A full explanation of the procedure to both child and parents is mandatory, including the length of time they will need to be in the hospital. The parents should be present during the test in order to support the child during the examination. The cooperation of the child can also be improved by the use of age-appropriate relaxation and distraction techniques. Furthermore, immobilization of the child during the test is essential in order to obtain high-quality images; this is often challenging, and in some instances sedation may have to be considered. The administered activity of the radiopharmaceutical is scaled on the child's body weight or body surface area.

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Clinical Indications

Measurement of gastric emptying is generally indicated in suspected gastroparesis, which presents with symptoms such as nausea, vomiting, early satiety, postprandial fullness, abdominal distension, or abdominal pain [3]. It can also be used in diabetics with poor control of their disease and in severe gastroesophageal reflux disease (GERD) unresponsive to medical treatment. Gastric emptying studies can also be used to confirm the suspected diagnosis of rapid gastric emptying (dumping syndrome), on the basis of symptoms occurring early in the initial hour after meal ingestion. The symptoms may include diarrhea, abdominal discomfort, nausea, bloating, and vasomotor symptoms.

Indications for small bowel and colon transit scintigraphy include, but are not limited to, evaluation of gastrointestinal and colon transit abnormalities as a cause of symptoms in patients with known or suspected gastroparesis, dyspepsia, irritable bowel syndrome, chronic constipation, chronic diarrhea, chronic intestinal pseudo-obstruction, and scleroderma. In the evaluation of patients with constipation, transit measurements may demonstrate a motility disorder or slow colon transit or may provide evidence to support a diagnosis of defecation disorder or functional outlet obstruction [5].

Radiopharmaceuticals

Tracers used in gastrointestinal motility studies have to be nonabsorbable and stable in gastric acid. For esophageal transit, gastroesophageal reflux (GER), and gastric emptying studies, the main tracers utilized are ^{99m}Tc-sulfur colloid or ^{99m}Tc nanocolloid. In a gastric emptying study, these tracers are used for both the liquid phase, as they bind well to milk, and the solid phase, as they have a good affinity for the protein matrix of the egg white. The maximum limit of the activity that can be administered varies according to different countries, ranging between 18 and 74 MBq [7, 8]. In the UK, the maximum limit is 40 MBq for studies evaluating esophageal motility and GER: this activity gives a maximum effective radiation burden of 0.9 mSv. For gastric emptying studies, the maximal activity is 12 MBq, which gives a radiation burden of approximately 0.3 mSv.

Diethyl-triamine-pentaacetic acid (DTPA) is used as a tracer for the liquid phase of the gastric emptying. ^{99m}Tc macroaggregates of albumin (MAA) can be used in the liquid phase of the gastric emptying study.

^{111}In-DTPA is frequently used as a tracer for the liquid phase of small bowel and colonic transit studies. The administered activity varies between 5.5 and 18.5 MBq in an adult. The maximum administered activity in the UK is 10 MBq, which gives a radiation burden of approximately 3 mSv. The administered activity in a child is scaled down from the adult activity in proportion to body weight, with activities ranging between 1.5 and 3 MBq typically administered in a child less than 10 years of age.

Esophageal Transit

Esophageal transit scintigraphy is a noninvasive method to qualitatively and quantitatively assess esophageal motility. It is fast and easy to perform with minimal radiation exposure. However, since its introduction by Kazam, several protocols have been used without standardization, thus limiting its widespread use [9]. Some protocols used in adults are applicable to older children able to swallow a bolus on command. Some variations have been introduced for assessing esophageal motility in young children and infants [10]. This test provides imaging and quantitative data on the transit of a radiolabeled bolus through the esophagus. It can be used for the diagnosis of organic and functional esophageal disorders and is especially valuable when performed serially to evaluate the effect of medical or surgical treatments.

The procedure is performed after a fast of at least 3 h in infants and 6 h in children. Any medication with a known effect on esophageal motility should be discontinued at least 72 h before the testing. ^{99m}Tc-sulfur colloid is routinely used for esophageal transit scintigraphy. In adults, the majority of the studies have been performed using a liquid bolus, whereas only few studies have used a semisolid bolus [11, 12]. In infants and children, an activity of at least 150 μ(mu)Ci (5.55 MBq) is added to 10 mL bolus of milk or water. In the case of milk allergy, a substitute may be used.

Infants can lie on a slightly inclined collimator. Older children can sit up with their back to the collimator. It is essential to turn the head of the bottle-fed infants to the side, to avoid superimposition of the radioactivity in the bottle over the upper esophagus. Older children can be fed with a cup or with a straw. Before the administration of the radiolabeled bolus, an external small radioactive marker is placed over the cricoid cartilage as an anatomical landmark. After a practice swallow with unlabeled liquid, the radioactive bolus is placed in the mouth and swallowed on command followed by a dry bolus at least 30 s later. Since some swallows are not completely propagated even in healthy subjects, 4–6 swallows should be obtained. The patient's position during the study can affect the results due to the effect of gravity. Performing the study with the patient in an upright position may be more physiological. Eliminating the force of gravity by performing the study with the patient in the supine position is more practical in infants and young children and more efficient in exposing motility disorders.

A large-field-of-view γ-camera fitted with a low-energy high-sensitivity collimator is used when imaging due to high temporal resolution required for quantitative studies. Dynamic images in a 128 × 128 matrix must be acquired in a rapid sequence. Because many of the events occur in a short time, images should be acquired at 4–10 frames per second for 60 s. The field of view of the γ-camera must include the entire esophageal tract including the mouth and the gastric fundus. An additional 10 min static acquisition is obtained when the patient is asked to dry swallow, in order to measure the clearance from the esophagus. If a large residual remains in the esophagus, delayed static images are obtained at 30 and 60 min. A Co-57 transmission image may be taken immediately or at 10 min following completion of the dynamic acquisition when the anatomical location of the tracer is uncertain (gastric fundus versus esophagus). Once the study has been completed, the images are reviewed in a one-to-one single-frame analysis and then played back in a cine display mode. This procedure depicts the dynamics of the swallowing and swallowing-related esophageal motor pattern and helps to identify aberrant patterns. For instance, the adynamic pattern is characterized by slow progression or even stopping of the bolus along the esophagus, such as in achalasia and scleroderma, whereas the uncoordinated pattern is characterized by random disorganized retrograde and antegrade or yo-yo contractions throughout the esophagus as occur in patients with diffuse esophageal spasm. This visual pattern corresponds to multiple peaks of the time-activity curves as determined by the quantitative assessment of the esophageal transit. Esophageal transit can be measured quantitatively with time and retention parameters. The esophagus is divided into upper, middle, and lower zones. Equal regions of interest (ROI) are placed on each zone and a fourth ROI is placed over the stomach. Time-activity curves for the proximal, mid and distal parts of the esophagus are generated. The curves allow quantitative and qualitative assessment of the bolus transit. Condensed dynamic images that summarize the whole deglutition event into one single image may also be used. A condensed dynamic image displays the profile of the swallowing event side by side on the *y*-axis, along with the time on the *x*-axis. The total transit time is usually calculated as the period between the first appearance of the tracer in the proximal esophagus and the time needed to obtain 90 % radioactivity clearance from the distal esophagus. The residual 10 % of the tracer is ignored in order to avoid any potential overlap with the tracer contained in the fundus. Besides total and segmental transit times, a clearance rate at time t is usually obtained with the following formula: $C = (E_{max} - E_t)/E_{max} \times 100\,\%$, where E_{max} is the maximal esophageal radioactivity and E_t is the radioactivity at time zero [10–12]. In healthy adults and in children, the pharyngeal transit is quite rapid occurring in less than 1 s. The normal transit time through the esophagus is typically less than 10 s, ranging from 3.4 ± 1 s for infants, 4.6 ± 1.9 for children aged 8–16 years, and 5.5 ± 1.1 for adults [13].

The sensitivity and specificity of the esophageal scintigraphy to detect esophageal disorders vary widely depending on the technique used and the esophageal disorder investigated. No diagnostic benefit of esophageal scintigraphy has been shown in patients with normal peristalsis even in the presence of severe motor abnormalities such as nutcracker esophagus or isolated hypertensive lower esophageal sphincter (LES) [14, 15]. On the other hand, several studies have shown its use in detecting abnormalities of esophageal peristalsis, such as achalasia, scleroderma, esophageal atresia, and diffuse esophageal spasm [16, 17]. It still represents an ancillary test when compared to esophageal manometry.

The main indications for esophageal transit scintigraphy are the evaluation of esophageal motility in patients who cannot tolerate manometry, the lack of availability of esophageal manometry, equivocal manometric results, and follow-up of patients with esophageal motor disorders such as achalasia and scleroderma (for instance, to assess the efficacy of surgical or medical therapy).

Gastroesophageal Reflux and Aspiration

Gastroesophageal reflux scintigraphy has been widely used for the evaluation of GER in children [18–20]. It is easy to perform, is well tolerated, and requires minimum patient cooperation. It also incurs a low radiation burden. Advantages of GER scintigraphy include the ability to detect pulmonary aspiration and to evaluate gastric emptying in the same study [21].

Technique

In young infants the radioactive milk should replace the normally scheduled feed, while older children should fast for at least 4 h prior to the test. The tracer used is ^{99m}Tc-sulfur colloid or nanocolloid (or ^{99m}Tc DTPA) mixed with an appropriate volume (between 30 and 240 mL) of milk or milk formula. The amount of activity administered is 0.55 MBq/kg, with a minimum activity of 7.4 MBq and a maximum of 40 MBq. The tracer is added to a portion of the patient's feed (one third to one half of the normal milk or formula feed volume). This volume is introduced into the stomach orally or alternatively by nasogastric tube (which should be removed after feeding) or by gastrostomy tube if this is the method used to feed. A second tracer-free volume is then given to complete the meal. The tracer-free volume has an important role of clearing residual tracer from the oropharynx and esophagus

prior to imaging. The volume of the feed varies according to the patient's age and weight. In most cases the desired volume is similar to the volume the patient is given for regular meals. The start and end of the feeding should be recorded.

There is no single universally accepted protocol for this study. Most protocols however share the same basic principles. After feeding, the child is positioned supine on the γ-camera couch. Young infants should be burped when possible prior to imaging. Restraints such as sandbags and Velcro straps may be used to secure young children to the imaging bed and prevent motion. Dynamic images are acquired from the posterior view with the stomach and chest in the field of view at a frame rate variable between 10 and 30 s/frame for 60 min [22]. Any event during the acquisition (motion, coughing, vomiting, reflux) is recorded at the time it occurs. The dynamic images are followed by anterior and posterior static views of the chest, with the stomach out of the field of view. These images are recorded on a 256×256 matrix over 3–5 min. It is important to perform the dynamic study over 60–120 min because a significant number of GER episodes can be missed by limiting the study to 60 min. The supine position is more sensitive than the prone position to detect GER [23].

Analysis

New appearance of tracer in the esophagus indicates an episode of gastroesophageal reflux. Placing markers over the shoulders, suprasternal notch and xiphoid is helpful in determining the level of reflux in the esophagus or oropharynx and in localizing possible activity within the lungs. Time-activity curves generated from ROIs placed over the esophagus can be helpful. GER episodes are seen as sharp spikes in the curves. Patient motion during the study can introduce significant artifacts in the curves, and therefore images should always be inspected for motion and motion correction should be applied when necessary. Visual inspection of the images in conjunction with time-activity curve and viewing of the study in cine mode is the most accurate way to read the study.

The presence of GER can be quantified using the formula: $R = E(t) - E(b) \times 100/\mathrm{Go}$, where R is the percentage of refluxed material in the esophagus, $E(t)$ the esophageal count at time t, $E(b)$ the para-esophageal background counts, and Go the gastric counts at the beginning of the study. R and $E(t)$ may refer to the entire organ and the individual regions [24]. According to this formula, the presence of a reflux >5 % is considered abnormal [19].

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 esophageal pH monitoring [20, 25]. Interestingly, scintigraphy has been shown to be more sensitive in the detection of reflux beyond the first postprandial hour as compared to pH monitoring, which usually fails to detect some types of reflux, especially when little or no acid is present [20]. Evidence of pulmonary aspiration is usually assessed through images obtained up to 24 h after administration of the radionuclide [21], but the sensitivity is low and a negative test does not exclude aspiration.

Clinical Indications

The lack of standardization and the absence of age-specific normal values limit the value of GER scintigraphy. This test does not confirm the diagnosis of GERD and therefore it is not recommended for the routine evaluation of children with suspected GERD. The test is recommended only in individuals with symptoms of gastric retention [26]. Multichannel intraluminal impedance and pH (MII-pH) monitoring can characterize the reflux episodes as acid or nonacid, as well as the level reached by the refluxate.

Gastric Emptying Study

Clinical Indications

The most common indication for a gastric emptying study is the evaluation of gastroparesis. The pathophysiological mechanisms underlining this condition are complex and still not well understood and include exaggerated fundal relaxation, poor antral contractility, lack of coordination between the antrum and pylorus, and pylorospasm. Presenting symptoms are typically nausea, early satiety, bloating, abdominal pain, and vomiting of undigested food. In a child presenting with symptoms suggestive of gastroparesis, it is essential to exclude an anatomical obstruction such as malrotation with a fluoroscopic upper GI contrast study. The radiological examination will also show the anatomy of the upper GI tract, the knowledge of which is very important to interpret the nuclear medicine study (where the anatomical details are poor), especially following a surgical intervention. The most common causes of gastroparesis in children are idiopathic, post-surgical, and diabetic. GERD can be also associated with gastroparesis. Assessment of possible dumping syndrome, based on symptoms occurring in the initial hour after meal ingestion such as diarrhea, abdominal discomfort, nausea, bloating, and vasomotor symptoms, is another possible indication for a gastric emptying study.

The test consists of a solid meal and/or a liquid meal. A solid meal is more reliable to assess gastroparesis. A liquid

meal can be normal in the presence of gastroparesis. However, recent reports suggest that both a solid and a liquid meal may be necessary [27, 28]. In very young children (younger than 3 years) a test feed based on milk or milk formula is considered to be adequate (milk is regarded as a semisolid meal, as it is a nutrient feed).

Patient Preparation

Medications that affect gastric motility should be discontinued for an appropriate period prior to the test depending on the pharmacokinetics of the drugs, unless the purpose of the study is to evaluate the effect of specific drugs on gastric motility. Typically, prokinetic drugs (domperidone, tegaserod, metoclopramide, erythromycin) are withdrawn for 48 h. Medications that delay gastric emptying, such as opiates and antispasmodics, are also stopped for 2 days. Serotonin receptor antagonists (5-HT-3) such as ondansetron, which have little effect on gastric emptying, can be given in case of severe symptoms of nausea and vomiting. Fasting blood glucose should be within normal range, due to the well-known effect of hyperglycemia on the gastric motor activity [29]. The child has to be kept nil by mouth for approximately 4 h. Young infants should miss a normal feed just prior to the test. Previous medical history, especially with regard to the GI tract, including previous surgical procedures, as well as a history of possible allergies, must be available before the study.

Technique

Liquid gastric emptying study: The feed is radiolabeled with ^{99m}Tc-sulfur or nanocolloid or ^{99m}Tc DTPA (the range of the administered activity is 10–37 MBq; the maximum administered activity depends on the legislation of the country). The amount of feed is calculated according to the patient's age and what they can actually ingest. The quantity of feed is split between the radiolabeled feed, that is ingested first, and a portion of unlabeled feed, that is drunk as a chasing portion to clear possible labeled feed that might have remained stuck in the oropharynx and esophagus. If the child is fed via a nasogastric or a gastrostomy tube, the amount of test feed introduced via the tube should reflect what the child could normally tolerate for their meals.

Solid gastric emptying study: The composition of the meal is a very important factor that affects the result of the study. The meal should consist of a balanced content of carbohydrates, proteins, and fat. Every effort should be made to stick to the standardized meal for a gastric emptying study (Table 14.1) [30]. If a child/adolescent is intolerant to eggs, an alternative meal has to be identified. There have been reports on different meals, based on cheese, chocolate crispy cake, and rice [31–33].

Table 14.1 Solid meal preparation

Recommended meal	
(a)	118 mL (4 oz.) of liquid egg whites (e.g., eggbeaters [ConAgra Foods, Inc.] or an equivalent generic liquid egg white)
(b)	Two slices of toasted white bread
(c)	30 g of jam or jelly
(d)	120 mL of water
Meal preparation	
(a)	Mix 18.5–37 MBq (0.5–1 mCi) of ^{99m}Tc-sulfur colloid into the liquid egg whites
(b)	Cook the eggs in a microwave or on a hot nonstick skillet (as described by Ziessman et al. (2007))
(c)	Stir the eggs once or twice during cooking and cook until firm—to the consistency of an omelet
(d)	Toast the bread and spread the jelly on the toasted bread

From Donohoe KJ, Maurer AH, Ziessman HA, Urbain JL, Royal HD, Martin-Comin J. Procedure guideline for adult solid-meal gastric-emptying study 3.0. J Nucl Med Technol. 2009;37(3):196–200, with permission

Image Acquisition

There is no single universally accepted protocol for this study. Most protocols however share the same basic principles. After feeding, the child is positioned supine on the γ-camera couch. Young infants should be burped when possible prior to imaging. Restraints may be used to secure young children to the imaging bed and prevent motion. Dynamic images are acquired from the posterior view, with the stomach and chest in the field of view, at a frame rate variable between 10 and 30 s/frame for 60 min [22]. Images are obtained in the anterior and posterior projections with the child supine on the gamma camera couch using a dual head camera. Continuous data recording is preferable over recording data only at discrete time intervals, as it gives information on the lag phase and may be helpful in identifying patterns of rapid gastric emptying; moreover, with the liquid phase, during the dynamic acquisition episodes of gastroesophageal reflux can be detected. Any event during the acquisition (motion, coughing, vomiting, reflux) is recorded at the time it occurs. The dynamic images are recorded on a 128 × 128 matrix and may be followed by anterior and posterior static views of the chest, with the stomach out of the field of view, with the purpose to assess for possible aspiration. These images are recorded on a 256 × 256 matrix over 3–5 min. Further delayed images at 2 and, if required, 3 h are obtained, using the same acquisition parameters as the dynamic acquisition, so that the delayed images can be compared to the dynamic series.

With a solid-phase gastric emptying study, a dynamic acquisition in the first hour is not strictly necessary, although it is helpful to assess the lag phase in the initial part of the study. It can also inform on the distribution of the radiolabeled feed within the proximal and distal portions of the stomach, and on possible to- and fro motion between the fundus and the antrum during the dynamic sequence, which may be due to dysmotility. The solid-phase gastric emptying study has to be continued with delayed imaging acquisition at least at 2 and 3 and possibly 4 h.

Image Processing

An ROI is placed around the stomach, as seen in the immediate post-feed image. A time-activity curve, corrected for decay, is generated from the stomach ROI. Motion correction should be applied when required. Care should be taken not to include bowel activity in the gastric ROI. Gastric emptying can be expressed as a percentage of the initial activity remaining at a specific time point (residual) or as the activity emptied by the stomach at these times. The pattern of the emptying curve is important, including the presence and the duration of the lag phase (seen in solid gastric emptying), which can provide evidence on abnormalities in gastric motility. Milk usually empties in an exponential or bi-exponential manner [19].

Analysis

The normal range of a gastric emptying study in the pediatric population has not been defined in detail. In particular, it is unclear whether the normal range is different in different age groups. This is due to the difficulty in performing gastric emptying studies in normal volunteers of pediatric age.

There is a consensus based on practice, but not scientifically validated, that a milk study is still normal if at 2 h the remaining activity in the stomach is 40 % or less of the initial gastric content. A solid-phase gastric emptying study in the adult practice, with the standard meal described in the guidelines based on radiolabeled egg white, is normal if at 4 h there is <10 % of the initial gastric content still present in the stomach [3, 4]. A detailed normal range for a specific meal and age group has not been defined in pediatrics. Also, it is not clear whether in grown up children and in adolescents a solid test feed is sufficient to estimate gastric emptying or whether both a solid and a liquid test feed are required. Preliminary evidence in the adult practice seems to suggest that both test feeds are required for a comprehensive assessment of gastric emptying [28]. Two examples of gastric emptying study are shown in Figs. 14.1 and 14.2.

Issues Requiring Further Evaluation

These are multiple. First of all, agreement has to be reached on an alternative meal to radiolabeled egg white for children intolerant of or unable to eat eggs. These alternative meals have to be validated; a normal range for different age groups has to be defined. The duration of the solid and liquid phases has to be clarified. Is it necessary to acquire images at 4 h in children? The effect of factors such as the volume (is the scan non-diagnostic below a certain volume of feed ingested?) and the composition of the test feed in carbohydrates, protein, and fat also have to be established. A "normal" range in postsurgical children (e.g., following Nissen's fundoplication) or in children fed via a gastrostomy tube has to be defined. It would be also interesting to see if gastric emptying scintigraphy can demonstrate the coordination of the different portions of the stomach (fundus and antrum, with relaxation of the pylorus) and provide some insights on gastric dysmotility, as hypothesized [24].

Small Bowel and Colonic Transit Studies

During the clinical evaluation of gastrointestinal symptoms suspected to be caused by a motility disorder, it may be difficult for clinicians to determine whether the symptoms are caused by upper or lower gastrointestinal tract dysfunction. In clinical practice, it is therefore helpful to evaluate motility throughout the entire gastrointestinal tract. At present, whole-gut transit scintigraphy (combined gastric emptying, small bowel transit, and colonic transit) is a relatively easy study to perform and, in some centers, is a frequently used and validated method to assess motility throughout the gut. Treatment selection may be guided by the finding of upper, lower, or combined gastrointestinal transit abnormalities. In addition, in patients with chronic constipation who are being considered for colectomy, an assessment of upper gastrointestinal motility is important since upper gastrointestinal dysmotility may reduce the clinical response to surgery.

Two techniques are used to evaluate motility through the GI tract, both of which involve irradiation of the subjects: transit of radio-opaque (plastic) markers viewed by X-ray and transit of radioisotope viewed by γ-camera (scintigraphy). Together, with the assessment of rectal evacuation dynamics and rectal sensation, the radioisotope studies of colonic transit represent the cornerstone investigations in patients with chronic constipation. These investigations have led to constipation being conceptualized into three broad and overlapping categories: normal transit constipation, slow transit constipation, and evacuation disorders. Transit studies per se address the question of whether the patient has a normal or delayed colonic transit.

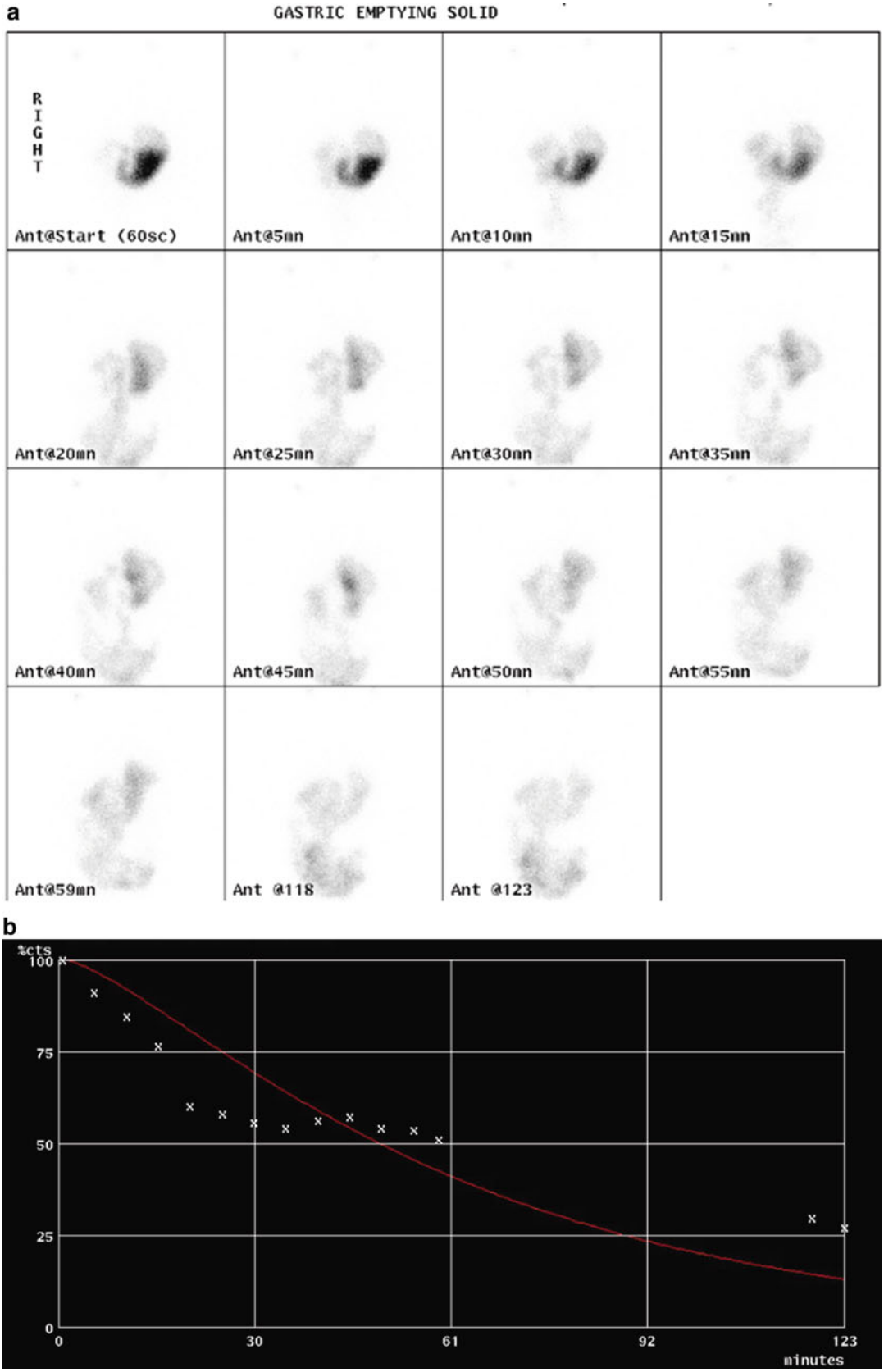

Fig. 14.1 (**a**, **b**) Gastric emptying study in a 2-year-old child with jejunal atresia and GERD. The dynamic acquisition over 1 h (**a**) shows little distribution of the milk-based radiolabeled test feed in the fundus of the stomach, with predominant distribution in the body of the stomach. The overall timing of gastric emptying is within normal limits. The delayed images at 2 h show further gastric emptying, with only approximately 25 % of the initial gastric content remaining in the stomach, as it can be seen from the time-activity curve (**b**). This study suggests impaired ability of the fundus of the stomach to relax after ingestion of the feed, which fits the clinical context

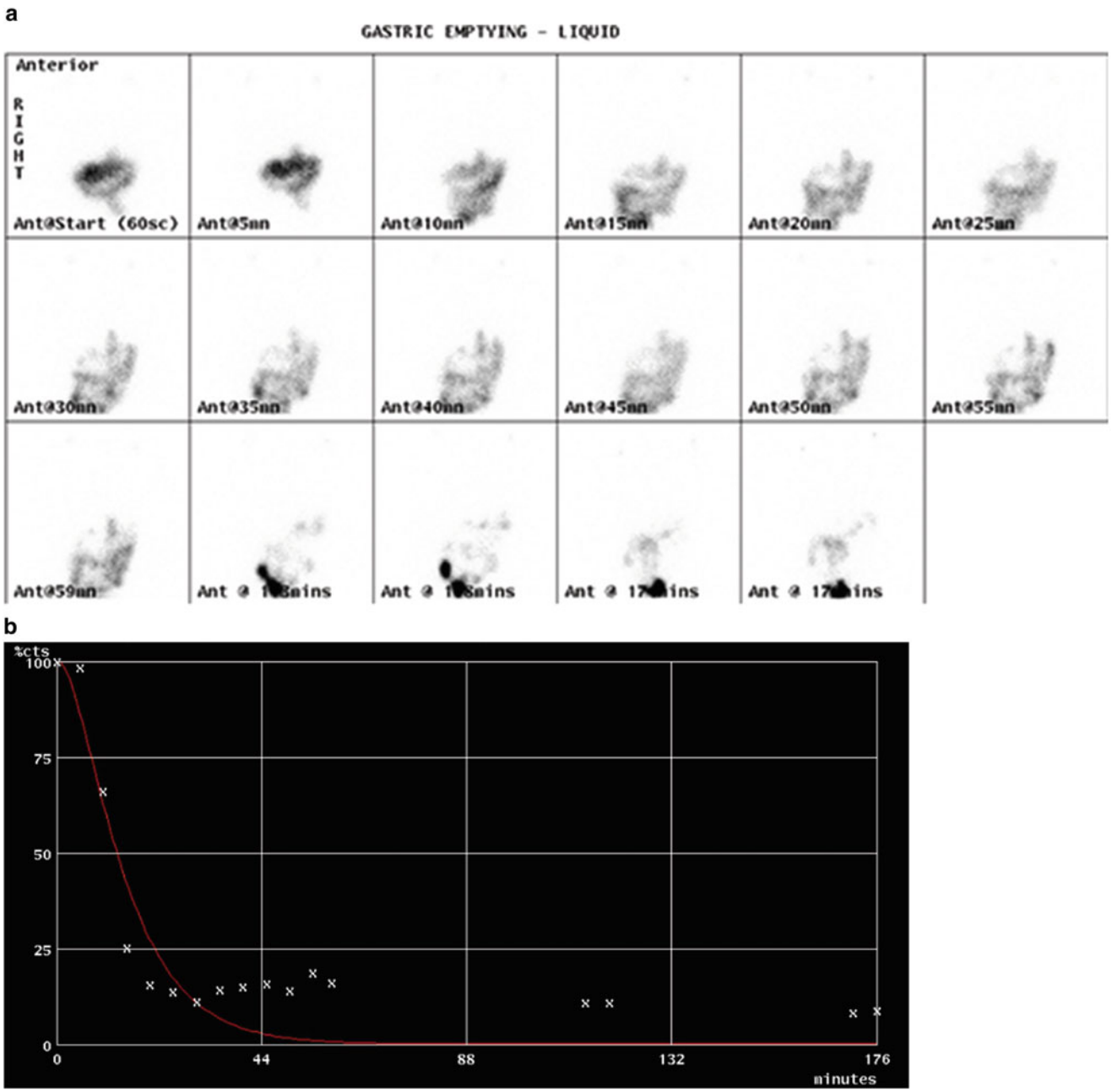

Fig. 14.2 (**a**, **b**) One-month-old baby with global developmental delay. The baby had a Nissen's fundoplication and was gastrostomy fed. The gastric emptying study shows a very rapid gastric emptying (**a**). The time-activity curve confirms that there is no significant activity remaining in the stomach by 35 min (**b**). This case is an example of dumping syndrome following Nissen's fundoplication

Common Clinical Indications

These include evaluation of gastrointestinal (GI) and colonic transit abnormalities as a cause of symptoms in patients with known or suspected gastroparesis, dyspepsia, irritable bowel syndrome, chronic constipation, chronic diarrhea, chronic intestinal pseudo-obstruction and scleroderma.

Patient Preparation

Medications that affect GI motility are withdrawn at least 2 days prior to the test, unless the purpose of the test is to assess the efficacy of these medications. These include opiate analgesics and anticholinergic medications (which slow gastrointestinal transit) and prokinetics (domperidone,

erythromycin, metoclopramide), which accelerate transit. For colonic transit studies, a bowel washout is performed prior to the test, to remove possible impacted feces. A radiological contrast study of the upper GI tract in order to exclude malrotation and clarify the anatomy of the bowel is essential in the interpretation of the GI transit scintigraphy, and this should be available prior to the acquisition of the radionuclide study.

Radiopharmaceuticals

The two main radiopharmaceuticals utilized in gastrointestinal transit studies are Tc-99m-colloid, to label the solid test feed for the evaluation of gastric emptying, and In-111-DTPA water to assess intestinal transit. A contemporaneous estimate of gastric emptying allows a more accurate determination of pure intestinal transit, especially if gastric emptying is slow and the clinical question concerns the evaluation of small bowel transit; this is why evaluation of gastric emptying is strongly advised in intestinal transit scintigraphy. A dual-isotope acquisition (Tc-99m-nanocolloid and In-111-DTPA water) can be performed.

Acquisition

The recently published guidelines on small bowel and colonic transit [5] suggest three options:

- A *whole-gut transit study*, which includes administration of a Tc-99m-colloid-labeled solid test feed together with In-111-DTPA water, to evaluate gastric emptying, small bowel transit, and colonic transit. Imaging is performed at hourly interval on the first day and then on days 2, 3, and 4 (and possibly 5, if needed).
- A *small bowel transit study*, with In-111-DTPA-labeled water for the small bowel follow-through and a Tc-99m-colloid-radiolabeled solid-phase test feed to evaluate gastric emptying at the same time (the solid-phase meal can be given with no radiolabeling, to create mass effect in the GI tract). Imaging is acquired at hourly interval up to 6–7 h on the first day, and then at 24 h to outline the large bowel, thus helping in the identification of the cecum and ileocecal valve.
- A *colonic transit study* with In-111-DTPA water: imaging is acquired at hourly intervals on the first day and then on days 2, 3, 4 (and possibly 5, if needed).

Markers placed on the patient's anterior superior iliac spine facilitate identification of the small bowel. Imaging is performed with the patient in an upright position using a large γ-camera equipped with a medium-energy collimator. During the dual-isotope acquisition, images are dynamically acquired for 1 h immediately after ingestion of the meal, with a static image at 2 h to measure gastric emptying of solid and liquids. Afterwards, images are usually taken at 4, 6, 24, 48, 72, and possibly 96 h. Images at 24 and 48 h may give a sufficient summary of colonic transit with acceptable specificity and high sensitivity for detecting motility disorders, although in constipated patients it is very helpful to acquire images at 72 h and, if activity is still seen in the colon, at 96 h [34]. Anterior and posterior images are obtained for an acquisition time up to 400 s on a 256×256 matrix. In the initial gastric emptying phase, the pulse height analyzer of the γ-camera is centered on 140 keV with a window of ±20 % to detect counts from Tc-99m and on two peaks (173 and 247 keV) ±20 % to detect counts from In-111. Subsequent images are acquired using the In-111 energy peak only.

Analysis

The commonest scintigraphic method for assessing small bowel transit is to measure oro-cecal transit time, defined as the time taken for 10 % of small bowel radioactivity to accumulate into the cecum [35, 36]. This is a very laborious method since it requires multiple images taken every 10 min until 10 % of the activity reaches the colon. A valid surrogate for the 10 % activity is the percentage of the administered activity reaching the terminal ileum at 6 h after meal ingestion.

The analysis of colonic transit is performed drawing different colonic ROIs on both the anterior and the posterior images in order to quantify the geometric center (GC). This represents the weighted average of radioactivity over specific regions of the bowel and determines the median point of radioactivity for each time point. The number of ROIs varies from 5 to 7, including the segment referring to the expelled stools. For instance, Southwell and co-workers defined six colonic ROIs each with a numerical value: (1) the small intestine, (2) cecum-ascending colon, (3) transverse colon, (4) descending colon, (5) rectosigmoid colon, and (6) excreted stools [34] (Fig. 14.3). A low GC indicates that the center of the activity is in the proximal colon, and a higher GC indicates that it has progressed to the left side of the colon and has been eliminated in the stool. In adults, based on this method, the normal mean (±1 SD) GC values range between 2.67 ± 1.09 to 4.6 ± 1.5 at 24 h, 3.89 ± 0.15 to 6.1 ± 1.0 at 48 h, and 6.6 ± 0.19 at 72 h [37]. In children, the normal mean ± SD GC values are 3.9 ± 1.1 at 24 h and 5.2 ± 0.9 at 48 h [38]. Of note, as a summary of the colonic transit, some researchers also utilize the emptying of the ascending colon expressed as $t½$ (time for 50 % emptying), which is significantly correlated with stool consistency.

To our knowledge there are few published data in children on small bowel and colonic scintigraphy [38]. Normative

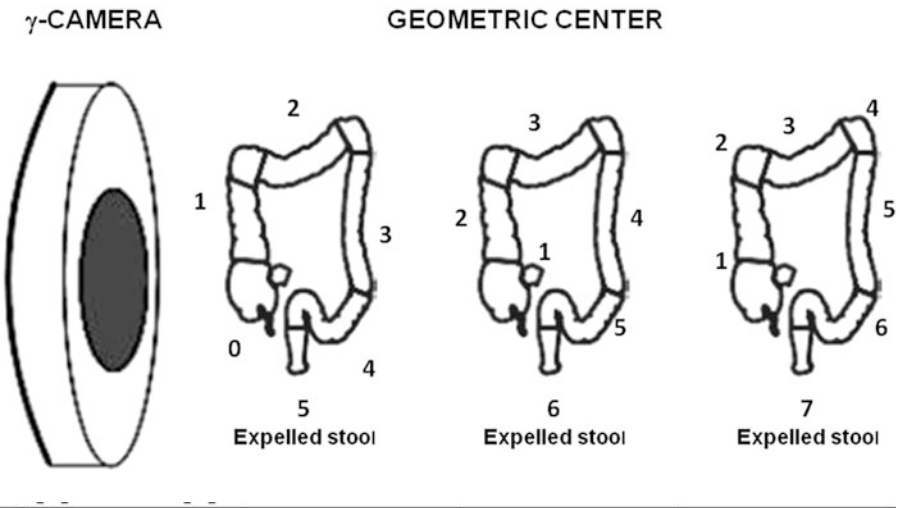

Fig. 14.3 Diagram showing the ROIs used to determine the geometric center of radioactivity in the colon

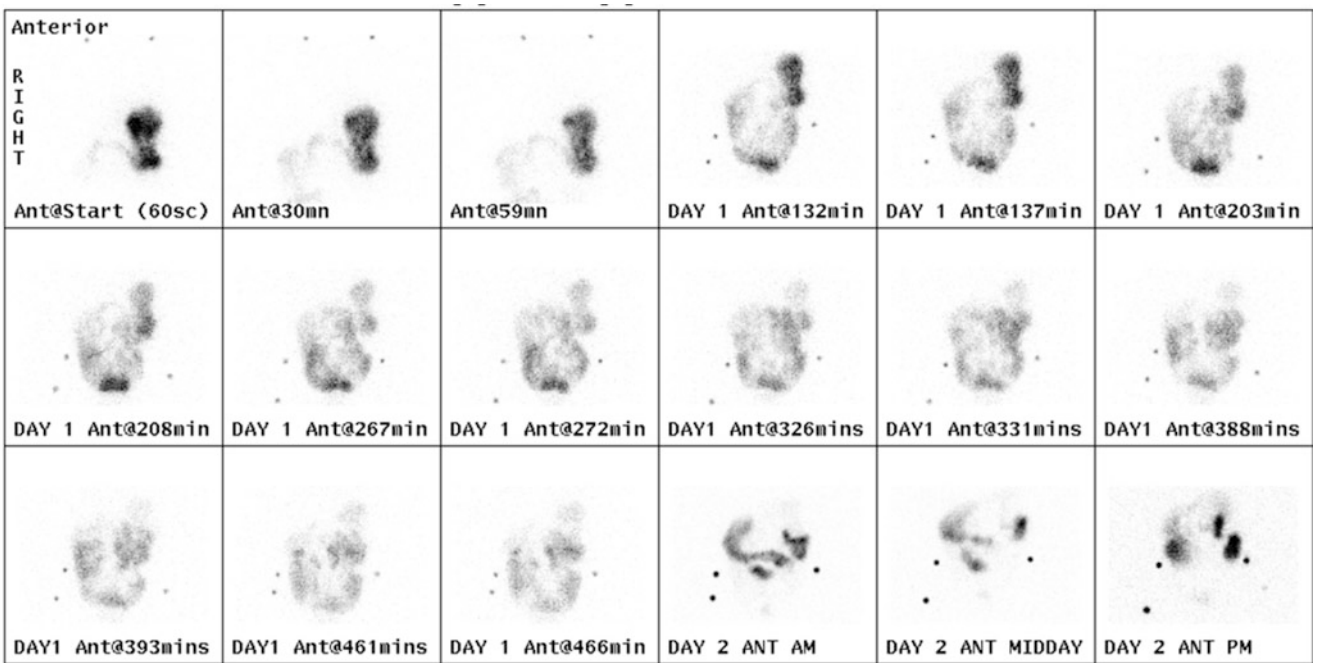

Fig. 14.4 A 15-year-old boy with a diagnosis of chronic intestinal pseudo-obstruction. Small bowel transit after ingestion of milk radiolabeled with Tc-99m-nanocolloid. Images acquired dynamically over 1 h to assess gastric emptying, followed by delayed images over 8 h on the first day, and then at 24 h to delineate the colon. The findings suggest slow transit through the small bowel

data in adults are limited; thus the test seems to be diagnostic only if extreme values are present. Identification of abnormal small bowel transit through scintigraphy has been shown to modify both initial diagnosis and clinical management, although its analysis needs to be interpreted with caution, keeping in mind that both delayed colonic transit and gastric emptying can affect small bowel transit.

Three categories of colonic transit could be readily distinguished also by visual assessment of the acquired images. In normal studies, the tracer reaches the cecum in 6 h and is largely excreted in 48 h. Slow colonic transit is identified when the tracer reaches the cecum at 6 h, but most radioactivity is retained in the proximal colon and transverse colon at 24, 36, and 48 h. In children with outlet obstruction or functional fecal retention, the tracer reaches the rectosigmoid by 24–36 h but is not passed at 48 h. In children and adolescents with refractory functional constipation, slow transit in the proximal colon occurs in 20–50 % and outlet obstruction in 22–55 % with some children exhibiting both patterns [39].

In quantifying colonic transit, scintigraphy can influence management of patients with refractory constipation who might benefit from different treatment strategies. For instance, by using colonic scintigraphy, the degree of efficacy of several prokinetic drugs can be evaluated. In addition, the type of surgery or stoma positioning may be determined by identifying the site of delay [40]. Examples of small bowel and colonic scintigraphy are shown in Figs. 14.4, 14.5, and 14.6.

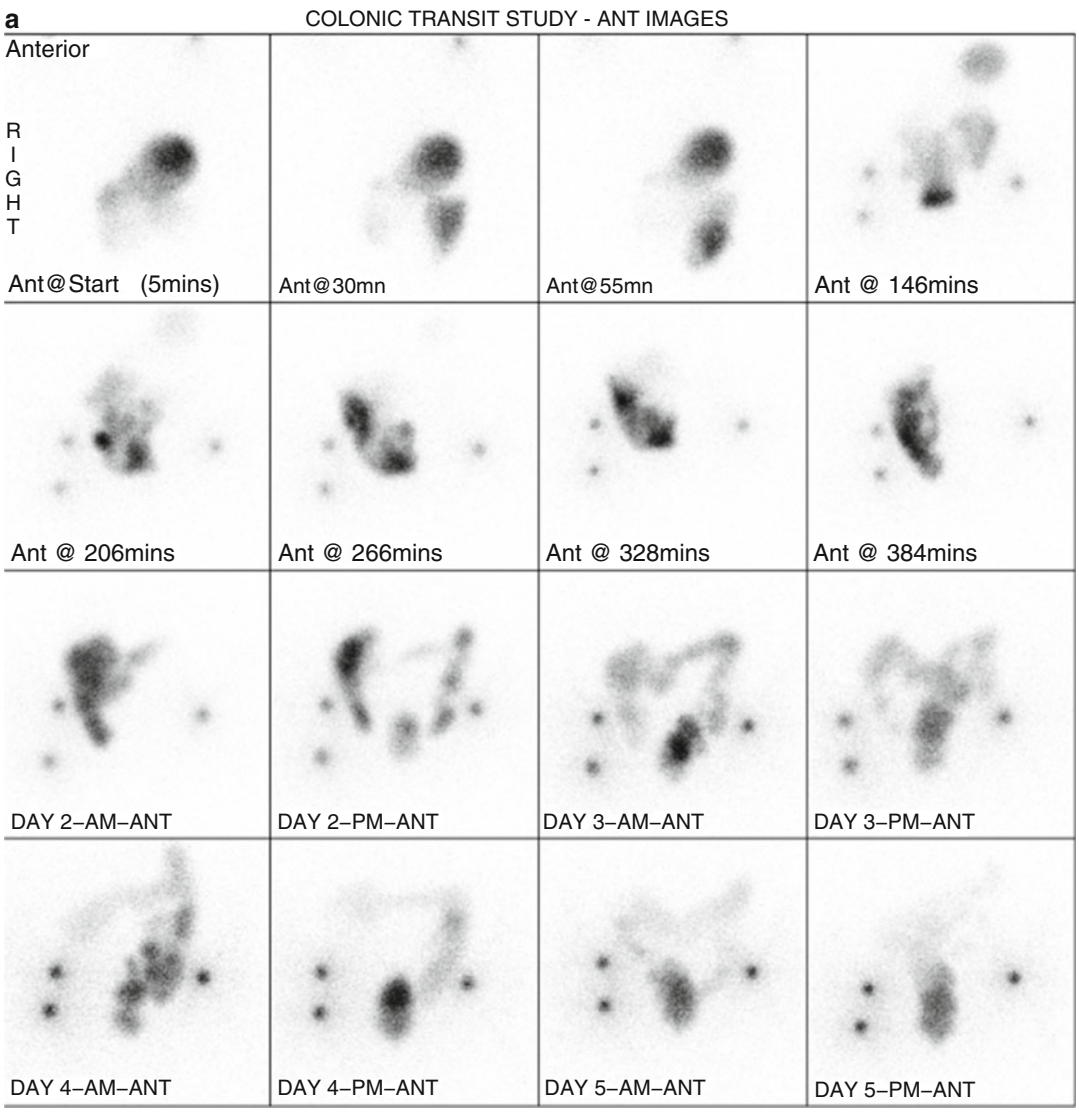

Fig. 14.5 (**a**–**c**) A 6-year-old girl with a family history of chronic constipation. Whole-gut transit study following ingestion of 2 MBq In-111-DTPA-labeled water and an unlabeled meal to create mass effect (**a**). The gastric emptying phase is slow; the transit through the small bowel is probably within normal limits, with activity seen in the right iliac fossa in the region of the ileocecal valve by 4 h. The colonic phase of the study shows hold up in the region of the sigmoid rectum, even 5 days after ingestion. This is confirmed in the time-activity curve (**b**). The center of gravity is lower than expected, confirming delayed transit especially in the descending colon and sigmoid rectum

Conclusion

Radionuclide studies of the GI tract provide a functional evaluation of intestinal transit and are an effective means of complementing radiological contrast techniques and manometry in the evaluation of the patient with symptoms of impaired GI motility. They are physiological, simple to do, and well tolerated. Their use in children is still in its infancy, mainly due to lack of standardization of the different protocols and smaller number of patients in comparison to the adult population. The gastric emptying study has been standardized in the adult practice and its normal range clearly defined. Procedure guidelines for the acquisition of the small bowel and colonic transit studies in adults have also been published. In the wake of these achievements, it is hoped that further evaluation of these studies will be performed in children and, as a result, their added value in the evaluation of GIT dysmotility will be clarified.

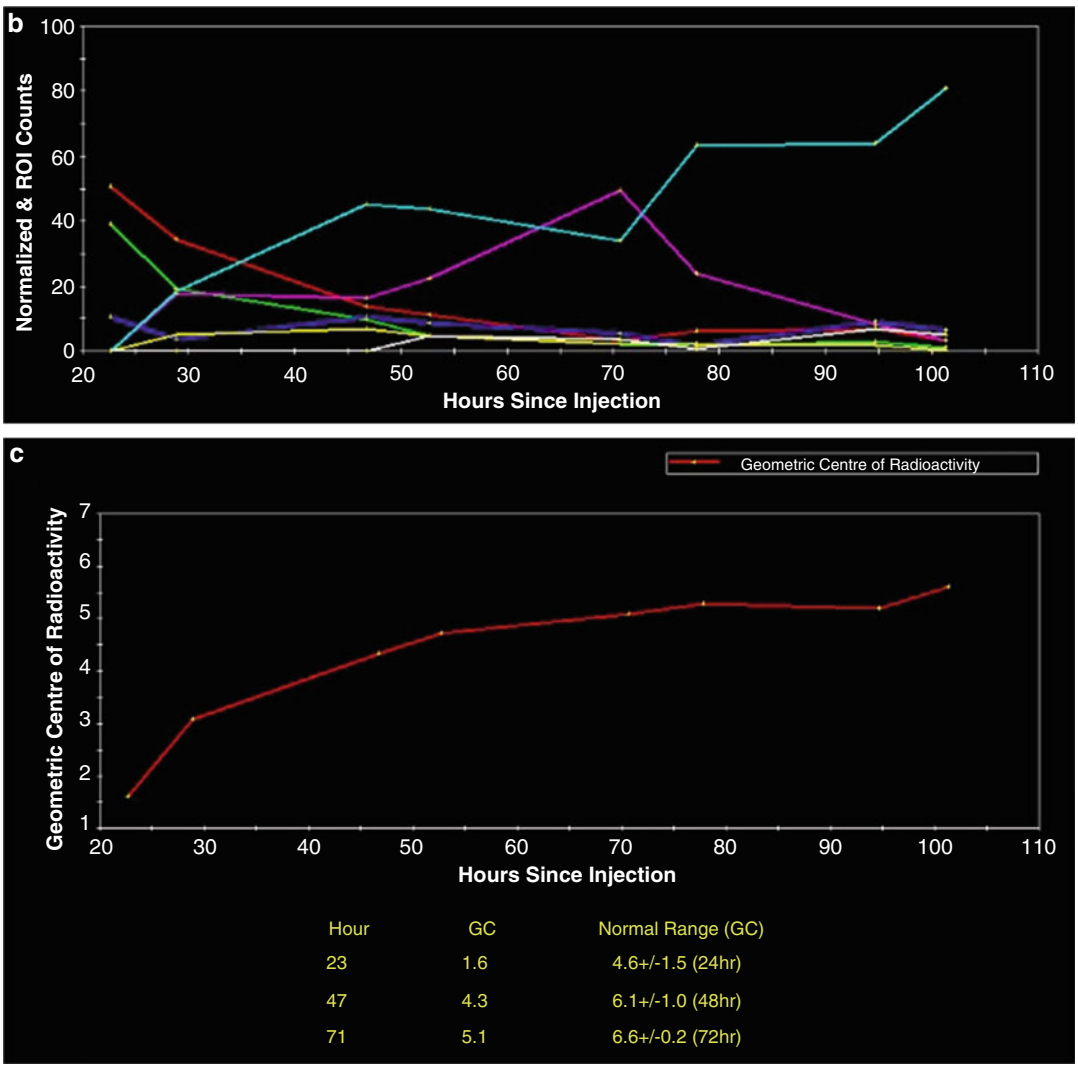

Fig. 14.5 (continued)

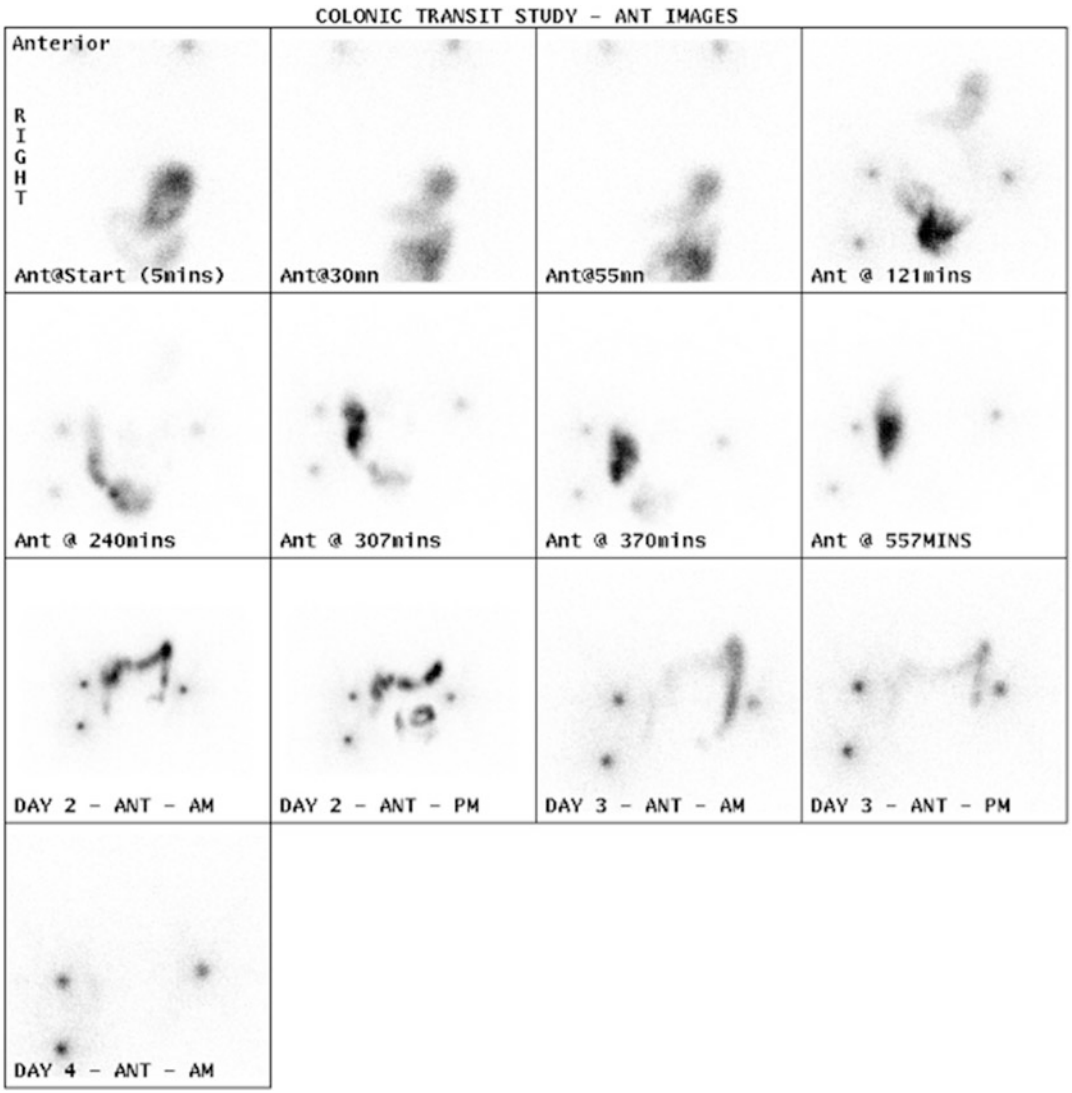

Fig. 14.6 A 12-year-old boy with severe constipation and rectal pain had colostomy and recent history of stoma pain and rectal pain. Colonic transit study after ingestion of 2.2 MBq In-111-DTPA water. Gastric emptying is probably delayed, with activity still seen at 2 h. Transit through the small bowel is normal. Within the colon, transit is probably within normal limits. This study suggests that colostomy has been beneficial in providing relief the severe constipation the child was complaining of

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15 Electrogastrography, Breath Tests, Ultrasonography, Transit Tests, and SmartPill

Ricardo A. Arbizu and Leonel Rodriguez

Electrogastrography

Electrogastrography (EGG) is a noninvasive test that records the gastric myoelectrical activity through cutaneous leads. The basis of the test is to identify the normal rhythmicity of the stomach of three cycles per minute (cpm), with a range of 2–4 cpm. This rhythm, which reliably corresponds to the slow waves generated by the gastric pacemaker, has been confirmed in animal and human studies by simultaneous electrode recordings from the gastric mucosa, gastric serosa, and skin [1–3]. Values above and below this range are called tachygastria and bradygastria, respectively (Fig. 15.1). The variables evaluated by EGG include the dominant frequency, the dominant power (amplitude in decibels), the percentage of normal frequency, and the percentage of coupling. The rhythmicity from other organs (like heartbeat and respiration) is filtered out during the recording, and motion artifact can be analyzed either visually or via a motion sensor and then manually excluded. The signal from all recordings is then selected and the EGG parameters are computed based on spectral analysis. This allows for an objective interpretation of the results. Since the first recording of an EGG in 1921 by Alvarez [4], multiple improvements have been added to this technique.

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In its early stages, most of the investigations with EGG were focused on its diagnostic role in peptic ulcer disease and gastric cancer and the physiological changes caused by gastric surgery. Over the last two decades, the focus has expanded to evaluate symptoms more than conditions. The first report of the use of EGG in children occurred in 1976, when Disembaeva et al. reported the normal EGG patterns in healthy children [5], followed by a report from Mirutko et al. describing its potential applicability in the evaluation and management of peptic ulcer disease [6]. The field of pediatric EGG exploded in the 1990s when the technique was evaluated in multiple disorders and symptoms.

Developmental Aspects

The gastric rhythm of 3 cpm seems to be irregular or absent at birth and matures over time [7, 8]. Although some have reported no difference between term and preterm infants [9], there seems to be agreement that the rhythmicity reaches adult characteristics in late childhood [7, 10].

Normal Values

Multiple studies, unfortunately following different methodologies, have attempted to develop normal values in children. The largest study was done by Riezzo et al. in 114 healthy children aged 6–12 years, which reported a gastric rhythm in the 2–4 cpm range and a significant increase in postprandial dominant frequency and power [11]. Another study with 55 healthy volunteers aged 6–18 years showed a mean dominant frequency of 2.9 ± 0.40 cpm preprandially and 3.1 ± 0.35 cpm postprandially, 80 % ± 13 % preprandial normogastria, and 85 % ± 11 % postprandial normogastria [12]. These normative values were independent from age, gender, body mass index, and position [11–13]. A recent study demonstrated that the adult norms reported by the

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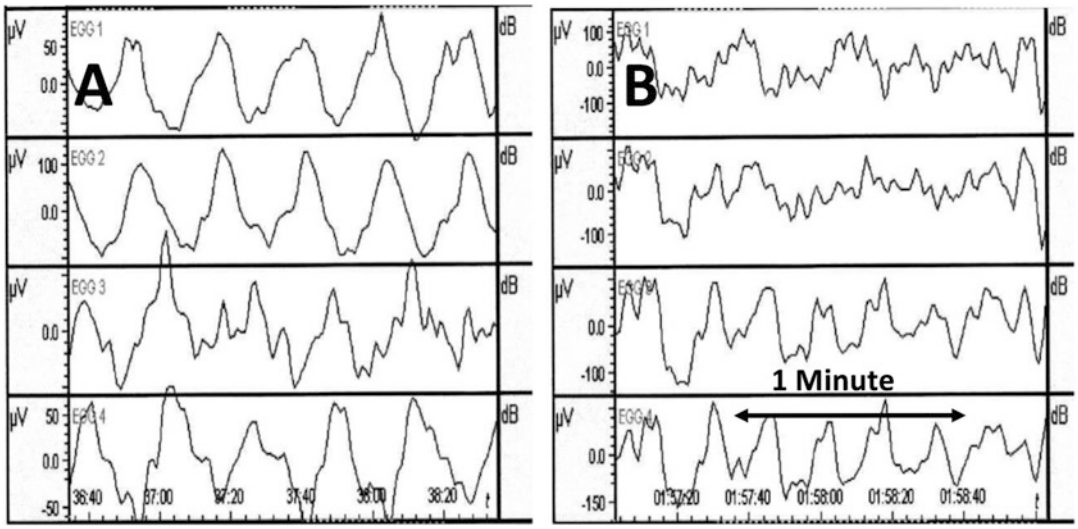

Fig. 15.1 *Electrogastrogram.* Parts of two electrogastrogram studies. (**a**) Shows normogastria or normal gastric rhythm of 3 cpm and (**b**) shows tachygastria with a rhythm of 5 cpm

American Neurogastroenterology and Motility Society can be used in children and adolescents when the same methodology is applied [14]. Among the factors that could affect the test values are the meal content and position. For infants, breast-feeding compared to formula feeding [15] and, for adults, solid meals compared to liquid meals [16], are associated with higher dominant frequency and power.

Clinical Applications

EGG has been considered as a substitute to other invasive tests, like gastric emptying scintigraphy and antroduodenal manometry, and also for other noninvasive but associated with operator-dependent downsides, like ultrasonography. However, most studies have not used the same methodology in terms of number and position of electrodes, recording time, test meals, and analytical software, limiting the validity of the test. Multiple studies in healthy adults as well as adults with specific disorders have shown no significant correlation between the findings on EGG and gastric emptying scintigraphy. Small series in children have replicated those findings [17]. EGG is not useful to discriminate between the three phases of the migrating motor complex (MMC) in adults [18], but it is helpful in differentiating children with normal or abnormal antroduodenal manometry. However, there is significant overlap in EGG results related to artifact from movement leading to inability to interpret data in up to 12% of patients [19]. Also, EGG findings do not correlate with gastric emptying and motility measured by ultrasound [20]. Rather than a substitute for these studies, EGG should be seen more as a supplement for the evaluation of patients with functional and motility gastrointestinal disorders.

Functional Gastrointestinal Disorders

Although some have reported that EGG may not be helpful in differentiating functional abdominal pain from gastritis [21], others have reported significant EGG abnormalities in children with functional dyspepsia and functional abdominal pain [22–24] particularly in patients with severe pain [22]. Also, EGG does not seem to be a helpful tool when it comes to distinguishing functional abdominal pain from peptic disease since chronic gastritis does not seem to be associated with gastric dysrhythmias [21, 25].

Gastroesophageal Reflux

EGG has been extensively used to assess the potential role of gastric myoelectrical abnormalities in gastroesophageal reflux (GER). In children, myoelectrical abnormalities associated with delayed gastric emptying seem to be associated with severe GER [26].

Chronic Intestinal Pseudo-obstruction

In children with chronic intestinal pseudo-obstruction, EGG has been reported to be abnormal [27], showing a significant difference in the values of either preprandial dominant frequency with tachygastria or differences in the postprandial value of 3 cpm when compared to normal subjects [28].

Eating Disorders

Gastric myoelectrical abnormalities have been related to the symptom pathophysiology in patients with eating disorders. Studies have shown that these abnormalities are more common in bulimia than anorexia nervosa [29] and in patients with long-standing disease [30]. EEG has been shown to be normal in early stages of anorexia nervosa [31].

Effect of Medications on Gastric Myoelectrical Activity

Prokinetic agents domperidone [32] and cisapride [33], unlike erythromycin [34], were effective in normalizing gastric myoelectrical activity in children. General anesthesia has been associated with significant gastric dysrhythmias that return to the baseline approximately an hour after anesthesia is stopped [35]. EGG has also been helpful to elucidate the potential mechanism of chemotherapy-induced emesis. Cytotoxic chemotherapy has minimal direct effect on gastric myoelectric activity in children who receive 5-HT3 antagonist prophylaxis. However, tachygastria was noticed during emesis episodes preceded by normal myoelectrical activity [36]. On the other hand, baseline abnormalities in gastric myoelectrical activity have been observed in patients who undergo high-dose chemotherapy and autologous stem cell transplantation despite normal gastric emptying scintigraphy and absence of symptoms [37].

Surgery

Nissen fundoplication may increase gastric myoelectrical abnormalities in neurologically impaired children. In part, this could explain the postoperative retching seen in some of these patients after fundoplication [38]. A study in children with neuromuscular scoliosis found that gastric myoelectrical power increased after surgical correction of spastic scoliosis, but the effect of surgery on gastric emptying, upper gastrointestinal symptoms, and nutritional status was minimal [39].

Strengths: Noninvasive, easy to perform, can be accomplished at bedside, no radiation required, not operator dependent.

Limitations: Non-standardized methodology, significant motion artifact.

Breath Tests

The most common indications for breath testing (BT) include assessment for lactose intolerance and small bowel bacterial overgrowth. The first is assessed by measuring breath hydrogen levels in response to lactose ingestion and the second by measuring breath hydrogen levels after an oral challenge with glucose or lactulose.

Recently, BT has been used as a noninvasive and nonradioactive alternative to the gold standard test for gastric emptying with scintigraphy. For this purpose, ^{13}carbon (^{13}C) isotope is used to label the substrate used for the oral challenge. The test is based on measuring the ratios of ^{12}C and ^{13}C. Both isotopes naturally exist in normal breath, 99 % as ^{12}C and 1 % as ^{13}C. This ratio is changed by the test meal enriched with ^{13}C resulting in expired $^{13}CO_2$. The exhalation of $^{13}CO_2$ in the patients' breath over time reflects the emptying of the substrate from the stomach. The substrates used for the evaluation of gastric emptying are ^{13}C-octanoic acid for solids and ^{13}C-sodium acetate for liquids. Recently, the ^{13}C-*Spirulina platensis* breath test has been validated and was compared to scintigraphy for gastric emptying in healthy volunteers [40–42].

BT has also been evaluated as an alternative to measuring whole gut transit (WGT). Lactulose has been classically used for this purpose. However, due to concerns of inherent transit acceleration by increasing the osmolality of the gut contents, other substrates have been used, including lactose (^{13}C-ureide breath test), and more recently, inulin has been found to be the most reliable substrate since it does not seem to affect gastric emptying [43, 44]. ^{13}C is typically measured in breath by continuous-flow isotope ratio mass spectrometry, although some have also suggested the use of nondispersive infrared spectrometry (IRMS) as a feasible method [45, 46]. The test relies on normal small intestine absorption, liver metabolism, and pulmonary function to validate the results. An important concern is the high inter- [47] and intrasubject [47, 48] variability. There is also significant inconsistency associated with the meal caloric content [49] in healthy adult volunteers, although some have reported very little intrasubject variability in critically ill subjects [50], making the test particularly attractive for this patient population.

^{13}C-octanoic acid has been reported as feasible [51], reliable, and reproducible in preterm [52, 53] and term infants [54], and results seem to be relatively independent from milk amount in preterm newborns during the first hours of life [53]. In healthy children, BT has performed poorly when assessing gastric emptying of both liquids [55] and solids [56], and a high day-to-day variability has been reported in the evaluation of WGT [57]. In preterm infants, gastric emptying measured by ^{13}C-octanoic acid BT does not seem to be affected by feeding osmolality, volume, or energy density; however, reducing osmolality and increasing feeding volume increases gastric emptying [58]. It is important to take into account the meal utilized for the study in children, as human milk [54] and hydrolyzed formulas [59] empty faster than partially and non-hydrolyzed formula. Another significant concern is the potential overestimation of gastric emptying by ^{13}C-octanoic BT due to gastric processing of the substrate. A correction factor of approximately 60 min has been classically added and validated in infants [60], while others have suggested the use of the Wagner-Nelson method [61]. BT with ^{13}C-sodium acetate for liquids and semisolids [62] and ^{13}C-octanoic acid for solid meals [63] has been validated for gastric emptying compared to scintigraphy. In adults, both the ^{13}C-sodium acetate [64] and ^{13}C-octanoic acid [65] do not seem to be affected by age, gender, or BMI. In a recent study, normal values for gastric emptying of a standardized test

milk-drink in healthy children were determined using the ^{13}C-acetate BT and concluded that the technique is reliable and well accepted by the patients [66].

Clinical Applications

Gastric Emptying

BT does not correlate with scintigraphy in functional dyspepsia [67] and could not discriminate between healthy volunteers and subjects with dyspeptic symptoms [68].

Gastroparesis

In children with gastroparesis, the one-half emptying time of ^{13}C-sodium acetate correlates with the time to empty half of radioisotope [69, 70] and also discriminates between healthy volunteers and children with symptoms due to gastroparesis [69]. BT has been reported as feasible in neurologically impaired children with GER [71]. BT can be done at bedside, which makes it useful under certain circumstances like in mechanically ventilated patients in the intensive care unit [72]. In a study of adult patients with diabetic gastroparesis, ^{13}C-octanoic acid BT was useful in discriminating between subjects with normal or delayed gastric emptying measured by scintigraphy [73].

Whole Gastrointestinal Transit

BT has demonstrated a constant WGT after the first month of age when a weight-adapted dose of lactulose is given [74]. The lactose-[^{13}C]-ureide breath test has been reported useful to evaluate WGT in children older than 8 months [75]. Results in healthy volunteers using lactulose BT have been reproducible [76], and this method has also been useful in the evaluation of small bowel transit (SBT) in patients with anorexia nervosa [77].

Strengths: Noninvasive, low cost, safe, office based, not operator dependent, no radiation required, useful in particular situations (pregnancy, intensive care setting, and infants)

Limitations: Requires normal intestinal, liver, and pulmonary function, poorly reproducible in children and adults, equipment may be expensive (IRMS)

Ultrasonography

Ultrasonography (US) is a noninvasive technique that can be used to evaluate gastric emptying, receptive accommodation, antral contractility, transpyloric flow, and gastric anatomical changes (volume and wall width) during meal and therapy challenges. US has been useful to demonstrate trituration of solids to small size particles, retention of larger particles with linear emptying of liquids [78], and antral motility coordination with pylorus flow during normal conditions [79]. Antral waves noticed on US correlate with peristaltic waves seen in antroduodenal manometry, with 99 % propagating aborally and 68 % becoming lumen occlusive at the site of the ultrasound marker [80]. US has been used in the evaluation of duodenogastric reflux in healthy volunteers [81] as well as in subjects with gastric ulcers [82]. The reproducibility in the assessment of gastric emptying is controversial with some studies reporting significant intra- and interobserver variability [83, 84], while others report differing findings [85, 86], but there is a common agreement on the significant day-to-day variability [85]. More recently, 3D US has been used to assess gastric emptying and has shown good correlation with scintigraphy in healthy subjects [87], but more studies are needed to validate the test.

Developmental Aspects

US has been invaluable in the evaluation of fetal gastrointestinal physiology demonstrating evidence of gastric emptying by 12–13 weeks [88], gastric filling and emptying by 20 weeks, and an important change in gastric volume by 25 weeks [89]. The frequency of these emptying cycles reaches a periodicity of 35–55 min by about 35 weeks [90] and demonstrates a clear normalization along pregnancy with cycles of longer duration and stronger power along the third trimester [91]. Gastric accommodation also seems to develop over time with preterm infants showing delayed gastric distention with feeds at 26 weeks, followed by a subsequent improvement by the time full feeds are tolerated, and almost immediate gastric distention with feeds by 32 weeks [92].

Clinical Applications

Gastric Emptying

The most common technique requires measurements by the same observer after fasting and at regular 30-min intervals postprandially. The emptying time is the time at which the antral area or volume returns to a baseline value [93], although others have also reported the half emptying time. US has shown a strong correlation with scintigraphy in assessing gastric emptying of liquids in healthy adult volunteers at rest [94, 95] and after exercise [96] as well as in subjects with diabetic gastroparesis [97]. In children, US has shown good correlation with scintigraphy; however, discordances associated to overlapping of the duodenum and stomach during scintigraphy and shadowing of the gastric antrum by air during US have been reported [98]. Establishing a safe preoperative fasting time has been another use of US in children after ingesting liquids [99] and in adults before undergoing anesthesia [100] and endoscopy [101]. US is reliable in assessing gastric emptying in preterm infants with a good correlation with intragastric volume [102] and particularly in

very low birth weight infants with nasal continuous positive airway pressure [103]. US is also useful during pregnancy when radiation should be avoided. Another advantage is that it allows for simultaneous assessment of gallbladder emptying [104]. US reliably assesses changes in gastric emptying in response to the use of prokinetic agents like domperidone [105–107], metoclopramide [108], cisapride [109], mosapride [110], and erythromycin [111].

Gastric Receptive Accommodation

US has emerged as an attractive alternative to the more invasive barostat to assess gastric accommodation. The test demonstrates no significant intra- and interobserver variability but moderate day-to-day variability in healthy adult volunteers [112]. It has been reported as a reliable tool to assess gastric accommodation in subjects with functional dyspepsia [113], children with recurrent abdominal pain [114], and the effect of therapy with prokinetic agents like mosapride [110] and other medications like sumatriptan [115].

Antral Motility

A novel use of US is to characterize antroduodenal motility associated with transpyloric fluid movement in healthy volunteers [116] and in subjects with GER symptoms [117]. Some have suggested an advantage of US by allowing a simultaneous observation of antral contractions and gastric emptying and have also reported a good correlation between antral hypomotility and delayed gastric emptying in patients with dyspepsia [118].

Strengths: Noninvasive, no radiation required, readily available, inexpensive.

Limitations: Reliable for assessment of liquids only, dissimilar and non-standardized methodologies, requires certain expertise, operator dependent, obesity and presence of air impair study interpretation (gaseous distention is common in gastrointestinal motility disorders).

Transit Studies

Several tests have been developed to assess gastrointestinal transit as an alternative to other more invasive and expensive tests associated with radiation, like scintigraphy transit studies. Here we describe tests to assess transit in different segments of the gastrointestinal tract.

Gastric Emptying

Paracetamol Absorption Test

The rate of paracetamol absorption measured by serial serum levels after oral ingestion has been used in multiple research studies as an indirect and noninvasive test to assess gastric emptying of liquids. The test has low interindividual variability [119] with good correlation with scintigraphy [120, 121] although recent studies have questioned this correlation [122]. It is not widely used in clinical practice due to the technical requirements of frequent blood draws, the cost of the assays, and the lack of sensitivity to assess gastric emptying in certain clinical situations [123, 124]. Its use has been relegated mostly to pharmacokinetic studies [125] and in special situations where radiation, mobilization, or meal intake are limited, like patients in the intensive care units [124] and during pregnancy [126].

Epigastric Impedance

This is a noninvasive method used for the assessment of gastric emptying/transit by measuring electrical impedance through skin electrodes. Results are comparable to scintigraphy [127]. The method has been revised and improved by adding applied potential tomography to generate tissue electrical impedance images and estimate gastric emptying and/or transit [128, 129]. Despite being an attractive noninvasive alternative, it is not widely used or recommended because of its low reproducibility due to significant motion artifact [130, 131]. In addition, the relationship between phasic contractions and phasic variations in impedance does not appear consistent enough to allow clinical application of the technique [132].

Radiopaque Markers

Radiopaque markers (ROM) have been extensively used in the evaluation of gastrointestinal transit due to their low cost, minimal radiation exposure, and uncomplicated performance and interpretation. Despite good correlation between gastric transit of ROM and gastric emptying measured by US [133], the test is not widely used due to the lack of standardization and the availability of other more reliable tests.

Intestinal Transit

Carmine dye, pellets, and ROM have been used in the evaluation of intestinal transit. Unfortunately, the correlation between these methods and scintigraphy is poor. Small intestinal transit is best assessed by scintigraphy, which is considered the gold standard, and wireless motility capsule. If these are not available, ROM should be considered.

Colon Transit

ROM studies have been used to evaluate colonic transit (CT) and several protocols exist for this purpose. The main drawback for ROM studies is the lack of standardization between

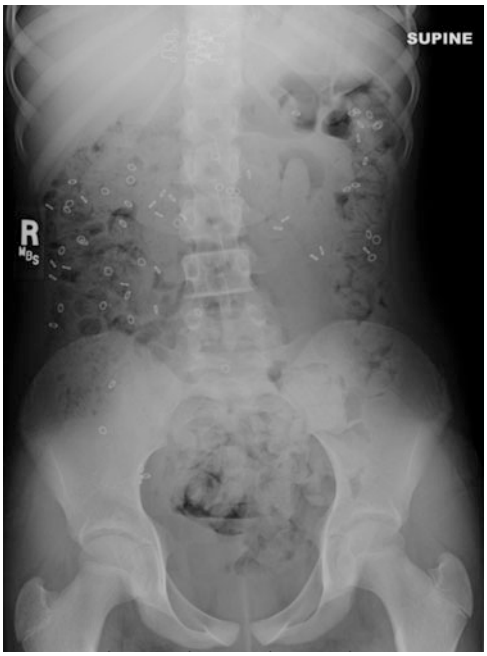

Fig. 15.2 Radiopaque marker study. This abdominal film was obtained on day 4 after ingesting three daily capsules with 24 markers each. Note the retention of all markers

the multiple methods and the centers performing the studies. The simplified protocol assesses normal vs. abnormal colonic transit. It requires the ingestion of a single ROM capsule (24 markers) on the first day followed by an abdominal film on the fifth day. Retention of >5 rings is considered abnormal. The Metcalf protocol (Fig. 15.2) is used for the same purpose with the added information on segmental transit, providing a broader extent of information. In this method, three sets of distinctive ROM capsules (24 markers per capsule) are ingested on three consecutive days followed by an abdominal film on the fourth day. Retention of >50 markers indicates delayed colonic transit. This protocol has shown good correlation with transit values obtained with other methods that require multiple films. The normal values for the test are total colonic transit 35.0 ± 2.1 h, right colon 11.3 ± 1.1 h, left colon 11.4 ± 1.4 h, and rectosigmoid colon 12.4 ± 1.1 h with overall shorter transit in men and no effect by age [134]. In children, norms by the Metcalf protocol have been established: total colonic transit time 37.8 ± 6.2 h, 10.8 ± 3.5 h for the right colon, 12.2 ± 2.7 h for the left, and 14.7 ± 2.1 h for the rectosigmoid [135]. The Metcalf protocol has been used to discriminate between constipated and non-constipated adolescents showing a statistically significant difference in total colonic and right and left colon transit times [136].

Transit measured by ROM seems to be faster than colonic transit measured by scintigraphy [137]. Overall, mean colon transit time does not differ significantly between young adults and children [137]. However, there are regional differences within the colon in relation to age, with children having faster transit times in the right and left colon and stagnation in the rectosigmoid [138]. In regard to clinical applications in children, ROM transit studies have been helpful to define pediatric slow transit constipation [139] and to demonstrate correlation between colonic transit and severity of symptoms [140], slower colonic transit in constipated children without soiling compared to those with soiling [141], rectosigmoid transit delay in low variety and global delay in high variety anorectal malformations [142], constipation in neurologically impaired children associated with slow colonic transit rather than fecal retention [143], and response to therapy for constipation [144].

Strengths: Readily available, minimal radiation, noninvasive, easy to interpret, inexpensive.

Limitations: Multiple non-standardized methodologies.

SmartPill

This novel device offers the ability to simultaneously measure contractility and transit. The SmartPill, or wireless motility capsule (WMC), measures 26.8 × 11.7 mm and has three different sensors that detect pressure (to measure contractility), pH (to measure transit from the stomach to small bowel and from the small bowel to colon), and temperature (to assess capsule exiting the body). The capsule is ingested orally with a standard meal and then the patient is discharged and wears a recording device for 3–5 days. The most important use of this device is to record pressures and simultaneously measure transit throughout the different segments of the gastrointestinal tract. In this regard, WMC has been used to evaluate gastric residence time (GRT), small bowel transit (SBT), colonic transit (CT), and whole gut transit (WGT) (Fig. 15.3). Perhaps the most significant contribution of the WMC in gastrointestinal physiology is the reaffirmation of the concept that nondigestible solids empty from the stomach primarily with the return of the phase III of the MMC when the fed state is over and the pylorus is completely open. No less important is the novel finding of gastric emptying of nondigestible solids in some subjects in association with high-amplitude antral contractions and not with the phase III of the MMC [145]. Since the WMC is an equivalent to a nondigestible solid, in healthy volunteers the gastric residence time moderately correlates with the gastric emptying of digestible solids measured by scintigraphy, and it is not surprising that there is a stronger correlation with emptying at 4 h than at 2 h [146, 147]. The WMC has been also useful to demonstrate the lack of effect of proton pump inhibitors on antral and small bowel motility and transit [148]. A great concern with transit studies with scintigraphy is the significant daily variability, which also potentially applies to the WMC. This has not been addressed in humans, but animal

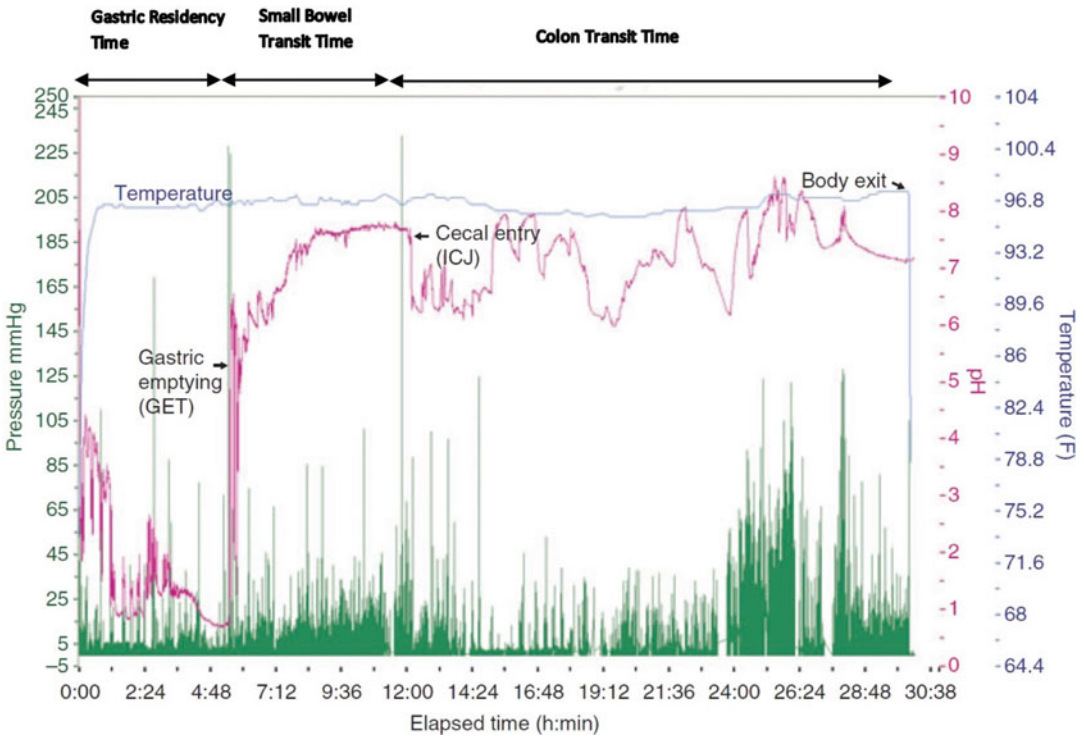

Fig. 15.3 SmartPill tracing. Notice the prolonged gastric residency time as well as significantly prolonged colonic transit (Courtesy of Dr. Braden Kuo and Dr. Margarita Brun)

studies have shown a significant variability of GRT by WMC and gastric emptying by scintigraphy with important intraindividual variability [149] and an inverse relationship between GRT and body weight [150].

Clinical Applications

Gastric Emptying

GRT measured by the WMC correlates with the gastric emptying measured by scintigraphy with higher sensitivity at 4 h than at 2 h [147]. WMC also has been useful to discriminate between healthy subjects and patients with diabetic gastroparesis [147] and to measure contractility assessed by number of contractions and motility index in the antrum and small bowel [151]. WMC has proven to be useful in classifying and diagnosing regional and generalized motility disorders with good agreement with other conventional motility studies [152]. A recent study by Green et al. compared the WMC with gastric emptying by scintigraphy and antroduodenal manometry in children with upper gastrointestinal symptoms. They reported a sensitivity and specificity of 100 % and 50 %, respectively, for the detection of gastroparesis by the WMC compared with the 2-h gastric emptying study. Both WMC and antroduodenal manometry were equal in detecting the presence of the MMC but the WMC was more sensitive in detecting motor abnormalities [153].

Constipation

Colon contractility is poorly characterized in adult patients with constipation and constipation-IBS. The WMC has been proven useful to measure contractility pressures in different segments of the gastrointestinal tract in these patients. A study by Hasler et al. that evaluated colon contractility and transit in healthy adult patients demonstrated greater pressures in the distal colon when compared to the proximal colon. In the same study, constipated patients with normal or moderately delayed transit showed increased motor activity that was partly explained by IBS. The findings in this study emphasize the differential effects on transit and motility in different constipation subtypes [154].

The WMC has been validated for measurement of the CTT and WGT by the simplified and Metcalf protocol. For the Metcalf protocol, a recent large multicenter study demonstrated that although the measured transit time was significantly different between the WMC and ROM, the agreement for delayed transit was 80 and 91 % for normal transit with an overall device agreement of 87 % [155]. The WMC with the simplified method showed slower GRT, SBT, CTT, and WGT in subjects with constipation compared to controls. Interestingly, the CTT was slower in women than in men and, more importantly, showed upper gastrointestinal transit delay in subjects with constipation [156]. In addition, the WMC has demonstrated that stool form predicts delayed vs. normal CTT in adults in contrast to stool frequency [157]

and has reiterated the concept of a generalized gastrointestinal dysmotility beyond the stomach in patients with gastroparesis by evidencing delayed CTT [158]. WMC has been also validated with scintigraphy for the evaluation of gastric emptying and colonic and whole gut transit (WGT) in healthy subjects as well as patients with constipation [159]. In regard to therapy outcomes, the only available study has demonstrated a possible positive effect on CTT and WGT by increasing dietary fiber [160].

Cystic Fibrosis

Patients with pancreatic insufficiency secondary to cystic fibrosis (CF) require optimal proximal intestinal neutralization of gastric acid for timely release of pancreatic enzyme replacement therapy. As mentioned above, the WMC has the ability to measure pH and transit in different regions of the gastrointestinal tract. A recent study by Gelfond et al. demonstrated delayed SBT and, more importantly, deficient proximal intestinal buffering capacity measured by WMC in adult pancreatic insufficient CF patients when compared to controls. This study also adds that measurement of gastrointestinal pH using the WMC may be a method to aid in the development of pharmacological interventions for patients with CF and potentially assess individualized interventions [161].

Strengths: Allows evaluation of transit of the whole GI tract and pressure measurements simultaneously, not operator dependent, ambulatory.

Limitations: Cost, availability, requires expertise in interpretation, risk of capsule retention causing obstruction, capsule size limits use in children, no studies have been done in children.

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Autonomic Nervous System Testing

16

Gisela Chelimsky and Thomas C. Chelimsky

The clinical utility of autonomic function tests in pediatric gastroenterology is steadily evolving. The current tests available evaluate cardiac and sudomotor responses and not direct gastrointestinal responses. Therefore, the results are interpreted and extrapolated (in the appropriate clinical setting) to the abnormality of the gastrointestinal tract. The tests are divided into those of autonomic cardiovascular function (cardiac response to deep breathing, Valsalva maneuver, head-up tilt (HUT) table test, handgrip, and cold pressor test) and those of sudomotor function (quantitative sudomotor test and thermoregulatory sweat test). Together, these two groups of tests evaluate the sympathetic adrenergic, sympathetic cholinergic, and parasympathetic cholinergic function in several organ systems and assess for the presence of a generalized autonomic neuropathy.

In preparation for the testing, the subject should be well hydrated and free of caffeine and nicotine exposure, and all medications that may interfere with the response of the autonomic nervous system should be stopped about five half-lives or 5–7 days prior to the testing date. Such medications include α(alpha)- and β(beta)-receptor agonists and antagonists, pro- and anticholinergics, mineralocorticoids, tricyclic antidepressants, selective serotonin reuptake inhibitors, and serotonin nonselective reuptake inhibitors.

Some data show altered electrical activity of the stomach in the upright position in subjects with postural tachycardia syndrome (POTS). In addition, treatment of the orthostatic intolerance in patients with POTS often benefits their gastrointestinal symptoms. These findings imply a significant physiologic relationship between orthostatic and gastrointestinal dysfunction, though the mechanism remains unknown.

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Autonomic Nervous System Testing

The role of autonomic testing in the evaluation and treatment of pediatric functional gastrointestinal disorders is slowly becoming established. At the simplest level, the autonomic nervous system constitutes the link between the central control of gastrointestinal function and the enteric nervous system. So far, no clinical tests directly assess the portion of the autonomic nervous system that innervates the gastrointestinal tract. Current routine clinical testing is limited to examination of cardiac, vasomotor, and sudomotor function, and based on the results of these tests in the appropriate clinical setting, the gastroenterologists or autonomic specialists must infer the potential role of the autonomic nervous system in the pathogenesis of gastrointestinal symptoms. The goals of this chapter are as follows:

1. To describe the current available autonomic testing and discuss the portion of the autonomic nervous system assessed by each test
2. To discuss the utility of these tests in clinical practice

Autonomic testing in children is increasingly available, though at this time still only a few centers perform more than just a tilt-table test. Although cardiologists may perform tilt-table tests, this is seldom performed in patients with primarily gastrointestinal complaints. This chapter describes the tests done most commonly in autonomic function referral centers (summarized in Table 16.1).

Tests Currently Available

The most common tests can be divided in two categories:

1. Tests of cardiovascular autonomic function:
   (a) Deep breathing
   (b) Valsalva maneuver

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Table 16.1 Tests of autonomic function

Autonomic test	Receptor	Afferent	Integrating center	Efferent signal
Deep breathing	Pulmonary stretch J-receptors	Vagus nerve	Nucleus tractus solitarius	Dorsal motor nucleus of the vagus (DMNX) to vagus nerve
Valsalva maneuver	Low-pressure atrial baroreceptors	Vagus nerve	Nucleus tractus solitarius	*Phase II*:
				1. Inhibition of DMNX HR
				2. Excitation VLM to descending sympathetics exiting at T1 vasoconstriction
				Phase IV:
				Reverse of 1 and 2
Tilt-table test	Low-pressure atrial baroreceptors	Vagus nerve	Nucleus tractus solitarius	1. Inhibition of DMNX to HR
				2. Excitation of VML to descending sympathetics exiting at T1 vasoconstriction
Sudomotor axon reflex test	Nicotinic cholinergic	Sudomotor nerve	None	Sudomotor nerve (axon reflex)
Thermoregulatory Sweat test	Temperature sensors in the anterior hypothalamus and peripheral veins	Temperature C-fibers	Anterior hypothalamus	Descending projections from anterior and lateral hypothalamus to intermediolateral cell horn preganglionic spinal neurons postganglionic sudomotor axons

DMNX, dorsal motor nucleus of the vagus; *VLM*, ventrolateral medulla

(c) Head-up tilt-table test
(d) Handgrip
(e) Cold pressor test

2. Tests of sudomotor autonomic function (sweating)
   (a) Quantitative sudomotor reflex test (QSART)
   (b) Thermoregulatory sweat test (TST)

The tests of cardiovascular autonomic function are particularly helpful in evaluating the branch of the autonomic nervous system involved (afferent baroreflex, or efferent sympathetic vs. parasympathetic), whereas the sweat tests provide information on lesion localization (central vs. peripheral nervous system). At this time, the pediatric norms are not well defined [1], and therefore, norms are inferred from adult values. Other tests of autonomic function such as pupillometry and pharmacologic evaluation of the baroreflex also exist; these are even less commonly utilized, have even less clearly defined norms, and therefore are not described in this chapter.

Deep Breathing

This test assesses heart rate variability, a parasympathetic nervous system function. The test is performed by instructing the patient to breathe deeply and regularly at a rate of 6 breaths per minute for 1 min. This is repeated after a minute of rest. Values for this parameter are age dependent, and a reduction in heart rate variability is considered abnormal. The authors utilize the data published by Ingall et al. [1] as age-based norms in their laboratory. The presumed purpose of the reflex is to provide adequate blood volume to absorb incoming oxygen during deep inspiration. When an individual inhales deeply, both air and vascular spaces expand and require increased lung blood volume. This need is met through an increase in heart rate during inspiration, triggered by vagal parasympathetic inhibition. When the individual exhales, the heart rate decreases, due to parasympathetic excitation [2]. In teenage years, this heart variability may become very large, probably due to high vagal tone. The nucleus tractus solitarius orchestrates this response to pulmonary stretch receptor afferents (J-receptors) [3] also accounting for baroreflex responses to blood pressure changes and intrinsic central respiratory rhythms.

Valsalva Maneuver

The Valsalva maneuver (VM) (Fig. 16.1) evaluates cardiac parasympathetic, cardiac sympathetic, and vasomotor sympathetic functions in response to low-pressure baroreceptor afferents from the right atrium and the great veins. The patient generates a continuous expiratory pressure of 40 mmHg by blowing against a fixed resistance and then suddenly releases the pressure after 15 s. This sudden high pressure in the chest cavity impedes venous return to the heart and reduces ventricular filling and stroke volume. Phase I and III are mechanical phases unrelated to autonomic physiology. During phase I, blood pressure rises for a few seconds as the held pressure is transmitted directly as a pressure wave through the vascular system. Phase II is a sympathetic nervous system-mediated response to the decline in cardiac output, resulting in vasoconstriction and tachycardia to restore blood pressure. The lost cardiac output is reflected in a drop in systolic pressure, while vasoconstriction causes a rise in diastolic pressure, resulting in a marked reduction in pulse pressure. When the subject releases pressure, blood pressure drops transiently during the mechanical phase III. The dominant effect occurs when blood fills the heart again, reaching higher levels than baseline, due to thoracic pressure normalization in the face of continued vasoconstriction. The baroreflex triggers a relative bradycardia through

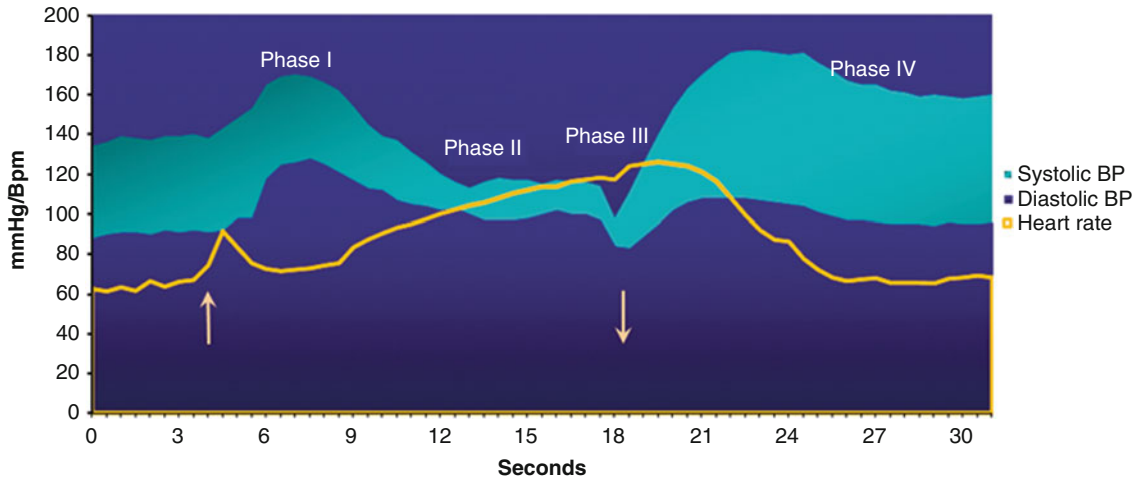

Fig. 16.1 Valsalva maneuver, showing the four phases and the blood pressure and heart rate changes of each phase

sympathetic withdrawal and parasympathetic excitation. Since vasodilation is slow, the blood pressure overshoots temporarily before returning to baseline. The result is usually read as a ratio of the fastest heart rate during phase II and the slowest heart rate during phase IV. If the ratio is below the age-based normal value, one must determine if this is due to an inadequate bradycardia during phase IV or inadequate tachycardia during phase II. In most centers, results of this study are repeated three times, with the two largest responses included in the dataset [2]. The values vary with age, and we currently utilize the pediatric values published by Ingall et al. [1].

Head-Up Tilt

This test evaluates sympathetic vasomotor responses. The patient must remain supine for a minimum of 10 min to obtain reliable baseline values and then passively tilted to 70°. The length of time of the tilt varies greatly across centers, being 10 min in many neurologic autonomic centers and up to 45 min when performed by cardiologists. Currently, in our institution, we tilt children without history of syncope for 30 min, and if there is a history of recurrent fainting, the tilt is extended to 40 min. In our clinical experience, many subjects would be diagnosed as normal had the tilt-table test been stopped at 10 min or may be erroneously diagnosed with POTS due to a cardioacceleration in the first 10 min, though this is not sustained in the ensuing time upright. The clinical significance of such findings is still unknown. A study performed by Carew et al. [4] in adolescents to adult age group (14–60 years) showed that 75 % of the subjects with complaints of orthostatic intolerance develop a sustained increase in heart rate to fulfill the heart rate criteria for postural tachycardia syndrome (POTS) within the first 3 min of head-up tilt and by 7 min had developed the diagnostic criteria for POTS. None of the subjects in the control group (no orthostatic intolerance symptoms) had sustained tachycardia. Thirty six percent of the subjects with POTS developed reflex syncope between 7.4 and 32 min into the head-up tilt [4]. This frequency of syncope in POTS is remarkably similar to that found by Ojha et al. of 38 % [5]. Based on these various data sources, perhaps children should be tilted for a minimum of 30 min, or less if they experience a pre-syncopal or syncopal event. Not every pediatric autonomic center agrees with this recommendation, and some tilt for 5–10 min. During the test, all symptoms should be documented (and rated on a numeric rating scale) so they can later be correlated with vital sign changes. It is of particular importance if children replicate their gastrointestinal complaints during the upright portion of the tilt test, as they will often benefit from treatment aimed at orthostatic intolerance [6].

The tilt-table test may demonstrate four patterns (Fig. 16.2): (a) normal response, (b) postural tachycardia syndrome (POTS), (c) orthostatic hypotension (OH), and (d) reflex syncope. In our clinical experience, children seldom demonstrate true orthostatic hypotension, while POTS and POTS associated with reflex syncope is the more common finding.

The Normal Response to a Tilt-Table Test

A normal tilt response includes a mild increase in diastolic pressure by 5–10 mmHg, a mild decrease in systolic blood pressure of 5–10 mmHg, and an increase in heart rate of about 10–20 bpm. A transient drop in blood pressure with reflex tachycardia within the first few minutes of tilt is common in healthy adolescents during tilt test [7].

Postural Tachycardia Syndrome

POTS is defined in adults as an increase in heart rate greater than 30 bpm within 10 min of becoming upright or to greater than 120 bpm, without a gradual drop in BP, and associated with orthostatic symptoms [8]. Singer et al. has demonstrated

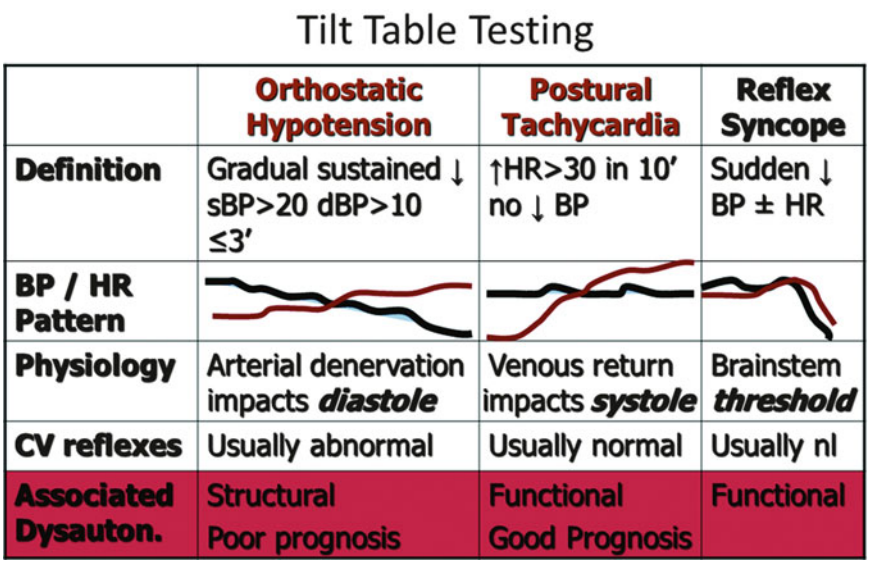

Fig. 16.2 This figure summarizes the different blood pressure (*black line*) and heart rate (*red line*) changes in the three orthostatic syndromes as well as the physiologic mechanism and a graphic description of the vital signs (*nl* normal)

that about 42 % of healthy pediatric controls have a heart rate increase during tilt of ≥30 bpm [9]. Based on these findings, most pediatric centers would diagnose POTS if the heart rate increases >40 bpm from baseline during the first 10 min of upright tilt, with associated orthostatic symptoms in the absence of significant drop in the blood pressure (systolic BP>20 mmHg and diastolic BP>10 mmHg). In children <13 years of age, the heart rate during head-up tilt should be >130 bpm, and in children >13 years of age, probably the adult value of 120 bpm may be applicable [9]. The mechanism involved in the pathogenesis of POTS symptoms is still unknown. However, the common final pathway is probably an excessive cardiovascular sympathetic activation perhaps secondary to abnormal blood volume distribution with venous pooling resulting in central hypovolemia and inadequate cardiac return [10].

Reflex Syncope

Other terms include neurally mediated syncope, vasovagal syncope, cardiogenic syncope, and vasodepressor syncope and emphasize different aspects of the event. It is defined as a temporary loss of consciousness caused by inadequate brain perfusion. It is produced by a sudden discharge from the medullary vasomotor center, decreasing sympathetic tone and increasing vagal tone and leading to peripheral vasodilation, hypotension, and bradycardia. Subjects usually experience a brief episode of loss of consciousness followed by rapid recovery and a relatively clear sensorium. It is important to note that syncope is a normal reflex that may occur in all subjects if enough strain is placed on orthostatic pressure maintenance (e.g., through the application of lower body negative pressure). Its probable function is the continued perfusion of the brain through gravitational mechanisms when the individual experiences severe loss of blood volume. Thus, the occurrence of syncope per se is not abnormal, but its occurrence at an inappropriate time is. Syncope and POTS can coexist, being present in 30 % of the children evaluated in our center. It is critical to distinguish the relatively acute increase in heart rate that may precede impending syncope from the chronic increase (throughout the entire tilt-table study) that occurs in POTS.

Orthostatic Hypotension

Orthostatic hypotension is defined as sustained drop in blood pressure of greater than 20 mmHg systolic or 10 mmHg diastolic within 3 min of being upright, associated with symptoms. The underlying pathophysiology is an impaired efferent sympathetic signal to the arterioles with consequent vasoconstrictive insufficiency [11]. Figure 16.2 graphically summarizes the three orthostatic syndromes and their etiopathology.

Sustained (Static) Handgrip

This test evaluates sympathetic vasomotor function and sympathetic cardiac and parasympathetic function. After baseline recording, the patient is instructed to sustain a grip at 30 % of their maximal grip strength for 3 min by squeezing a hand dynamometer. Heart rate and blood pressure are monitored continuously from the contralateral upper extremity. The maneuver results in both cardioacceleration and an increase in blood pressure. In contrast to the tilt-table test and the Valsalva maneuver, the afferent signal here originates from muscle and is related to lactate accumulation, in contrast to the former two tests where the initial afferent signal originates from the low-pressure baroreceptor in the right atrium. An early heart rate increase is due to vagal withdrawal, and a later heart rate response is due to sympathetic activation. The blood pressure increase is due to both increased cardiac output and to sympathetically mediated arterial vasoconstriction [12].

Quantitative Sudomotor Reflex Test

This study evaluates for an autonomic neuropathy through the presence and function of postganglionic sudomotor axons. Though innervated by the sympathetic nervous system, acetylcholine is the postganglionic neurotransmitter to the sweat gland. The test is performed by applying a capsule with dual concentric chambers to the patient's skin. Acetylcholine from the outer chamber is iontophoresed into the skin and via an axon reflex stimulates axons that innervate the local sweat glands. The axon reflex stimulates more distant sweat glands whose output is then measured in the area of the central chamber of the capsule. The capsules are usually placed from distal to proximal on two sites on the upper and lower extremities, respectively, though other groups use three capsules in the lower extremity and one in the upper [12]. A reduced response indicates postganglionic sympathetic sudomotor impairment. The sudomotor reflex is preserved in central nervous system processes.

Thermoregulatory Sweat Test

This study helps to differentiate a central disorder from a neuropathy or radiculopathy. It evaluates both preganglionic and postganglionic pathways. The patient dressed in a disposable swimsuit-like garment is covered with a powder that changes color on contact with moisture. The subject is placed supine in a sauna-like enclosure and kept at an air temperature of 50 °C, with a relative humidity of 50 %. The skin temperature is maintained between 38.5 and 39.5 °C. The skin may also be heated with infrared heaters. The test is interpreted based on the detection of areas of lack of sweat (anhidrosis) [13]. Usually a subject with central disorder will have lack of sweating all over the body, although sweating on hands and feet may be preserved. Reduced sweating in the toes and fingers with a distal to proximal gradient is suggestive of a peripheral process. If there is lack of sweating following a nerve root pattern, the study may suggest a radiculopathy.

Critical Steps in Preparation for All Autonomic Function Testing

Prior to testing, the patients should be asked to have a normal meal at the usual mealtime with plenty of fluid. They must also taper or stop all medications and dietary or nutritional supplements that may influence test results. This includes caffeine and passive or active exposure to nicotine. When the patient is unable to avoid taking some medications, results need to be interpreted accordingly. Each center has protocols for when and which medications should be stopped. As a general guideline, α(alpha)- and β(beta)-receptor agonists and antagonists, pro- and anticholinergics (particularly phenothiazines and tricyclic agents), and mineralocorticoids (including fludrocortisone) must be discontinued at least five half-lives prior to testing. Selective serotonin reuptake inhibitors (SSRI) and serotonin nonselective reuptake inhibitor (SNRI) agents should be discontinued 5–7 days prior to the testing.

Utility of Autonomic Testing in The Evaluation of Children with Functional Gastrointestinal Disorders and Motility Disorders

To date, autonomic testing in children has been deployed in limited ways, being primarily utilized in the evaluation of rare disorders such as familial dysautonomia. The utility of autonomic testing in functional gastrointestinal disorders (FGID) is emerging. More than 15 years ago, the first case series was reported of children with FGID, demonstrating a postural tachycardia in most subjects and an autonomic neuropathy in many. The cardiac parasympathetic function was preserved in all subjects [14]. A few case reports further supported this association and reported improvement of the gastrointestinal symptoms when treatment was aimed at the orthostatic intolerance [15, 16]. A few years later, Sullivan and collaborators reported tilt-table results in 24 children with FGID [17]. These children had symptoms of abdominal pain (71 %), nausea (56 %), and vomiting (50 %). The tilt table showed POTS in four, POTS and neurally mediated hypotension (termed reflex syncope in this chapter) in eight, and neurally mediated hypotension alone in 12. In about half of the cases, the tilt-table test reproduced the gastrointestinal complaints. Follow-up was available in 18/24. Twelve children were treated with fludrocortisone (four had also sertraline) with either improvement or resolution of symptoms [17]. A retrospective study supported the concept that children that replicate the gastrointestinal symptoms during the tilt-table test usually had POTS and often show improvement of gastrointestinal symptoms when treated with fludrocortisone [6]. Fortunato et al. added stronger prospective data in 16 children with orthostatic intolerance and nausea (mean age 14.8 ± 2.8 years), for whom treatment with fludrocortisone 0.1–0.2 mg daily for >4 weeks significantly improved nausea, dizziness, abdominal pain, flushing, and missing school, but interestingly did not improve vomiting, syncope, constipation, and anorexia [18]. Given the high association of nausea and POTS, a few studies have evaluated the prevalence of gastroparesis in children with POTS. Patients with POTS and with FGID typically demonstrate normal or accelerated gastric emptying, delayed only in a minority [19, 20]. A pediatric study comparing the gastric emptying time in patients with FGID with POTS vs. those without POTS showed no significant difference [21].

In an attempt to further understand nausea and foregut symptoms, the association of electrogastrographic changes

were assessed in subjects with and without POTS in the supine position and during the upright portion of the tilt test. The study found that in the upright position, children with POTS developed more gastric electrical abnormalities in the locations corresponding to the fundus and the antrum, while the opposite happened in the non-POTS group [22]. These findings suggested a possible mechanism for the association between orthostatic intolerance and the gastrointestinal symptoms, mainly when symptoms are replicated in the upright position. Further prospective, blinded studies will determine if treatment aimed at the orthostatic intolerance is superior to "conventional" treatment of FGID or to placebo in this subgroup of children who have FGID symptoms replicated while upright. Against the concept of placebo response, most children have failed all "conventional" gastrointestinal treatments prior to referral to our center. Sullivan and collaborators reported that tilt table was performed after having symptoms for more than a year, sometime even 3 years (48 %), and had failed gastric acid secretory blockers, antispasmodics, and prokinetics. Many of them (50 %) had been referred to a psychiatrist or psychologist for their symptoms, having then resolution with fludrocortisone or sertraline [17]. One would not expect a placebo effect to be restricted to orthostatic agents.

But POTS does not explain all the symptoms and comorbidities. A recent study showed that in a tertiary care center, children and adolescents seen at the pediatrics autonomic clinic showed the same comorbidities whether or not they had POTS. Comorbidities included fatigue, sleep problems, dizziness, gastrointestinal symptoms meeting Rome criteria for FGID, migraines, chronic nausea, fibromyalgia, and joint hypermobility [23].

Practitioners often wonder if anxiety may be the primary cause of the increase in heart rate during tilt table test. Masuki et al. attempted to answer that question by performing graded venous pooling with lower body negative pressure by wearing antishock trousers to −40 mmHg and sham venous pooling by inflating the trousers to −5 mmHg and vacuum pump activation without lower body negative pressure in subjects with POTS and in controls [24]. They also performed mental stress to determine if there were differences in the heart rate increase in the two groups. They demonstrated that only significant venous pooling caused a rise in heart rate in the POTS group, whereas the heart rate increase in response to "sham" venous pooling and mental stress was not significantly different between the two groups. These results suggest that the heart rate increase in patients with POTS is not related to anxiety but rather to reduced venous return to the heart [24].

Although many of these studies are either retrospective or small series, evidence is slowly mounting for the role of autonomic dysfunction in children with FGID and hence a benefit of autonomic testing in the evaluation of children with FGID. Prospective studies will compare different treatment modalities and determine if fludrocortisone, salt supplementation, and beta-blockers may benefit the gastrointestinal symptoms.

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Part III

Disorders of Digestive Motility

Pathology of Enteric Neuromuscular Disorders

17

Raj P. Kapur

Diagnosis and management of patients with intestinal dysmotility is best conducted by a multidisciplinary team, including a pathologist with interest and experience in enteric neuromuscular disorders. While most pathologists are familiar with the key diagnostic features of Hirschsprung disease, and will recognize advanced histopathological signs of visceral myopathy, many are not familiar with subtle features that correlate with the myriad of etiologies and evolutionary stages of gastrointestinal neuromuscular pathology (GINMP). In addition, common alterations caused by tissue handling or nonspecific adaptations to obstruction may be misinterpreted by the uninitiated in their zeal to explain a patient's symptoms. Even GINMP experts are unable to identify specific changes in many tissue samples from patients with profound dysmotility, in part because etiologies are diverse and likely include physiological defects that cannot be resolved with routine histological, immunohistochemical, or electron microscopic methods. The field is compounded by the fact that considerable published pathological descriptions are often anecdotal, conflicting, and confounded by ambiguous or imprecise clinical terminology. Optimal patient care necessitates that pathologist and clinician are aware of these limitations and apply an evidence-based approach to each patient, with a clear understanding that in some cases management decisions will be based on negative pathological findings and clinical "best judgement."

This chapter is written primarily for surgeons and gastroenterologists who treat patients with motility disorders, to help them formulate realistic expectations from pathological investigations and understand how such investigations impact on clinical management. The author aims to provide the basic information necessary to choose a diagnostic procedure, obtain an adequate tissue sample, and deliver it in an appropriate state to the pathology laboratory. Guidelines are presented for how tissue samples should be handled in the laboratory to resolve most types of GINMP and allow for consultation and/or special studies if indicated. Histologic features, diagnostic pitfalls, and ancillary methods are discussed for Hirschsprung disease and a subset of common causes of chronic intestinal pseudo-obstruction (CIPO), but comprehensive coverage of all forms of GINMP is not attempted. The reader is specifically encouraged to consult other references for more information on the enteric neuromuscular pathology of systemic muscular dystrophies (e.g., myotonic dystrophy, Duchenne muscular dystrophy) [1, 2], esophageal achalasia [3], gastroparesis [4, 5], and systemic connective tissue disorders [6]. Although some patients with severe CIPO are treated by intestinal allograft, transplant pathology is reviewed elsewhere [7].

Rectal Biopsy and Diagnosis of Hirschsprung Disease

Rectal biopsy is one of the first diagnostic procedures performed in many patients with impaired intestinal motility, particularly when clinical signs date back to birth. The primary purpose of rectal biopsy is to exclude Hirschsprung disease (HSCR)—congenital aganglionosis of the distal rectum and a variable length of contiguous bowel (see Chap. 24). Other conditions that may be diagnosed or strongly suggested by rectal biopsy include intestinal neuronal dysplasia type B (IND), neuronal intranuclear inclusion disease, some mitochondriopathies, and some forms of visceral myopathy (requires full-thickness biopsy). Apart from HSCR and IND, rectal biopsy is not a sensitive diagnostic approach to the other conditions, but is less invasive than other types of intestinal biopsy.

Two types of rectal biopsy, suction and "full-thickness," are used. Suction biopsies are obtained with a special instrument designed to liberate and capture a small sample of rectal mucosa and underlying submucosa. Suction rectal biopsy can be performed without anesthesia and from a neonate and is the procedure of choice to exclude HSCR in patients under a year of age. For older patients, suction biopsy does

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not harvest as much submucosa, possibly because the tensile strength of submucosa increases with age. Therefore, many clinicians opt for a full-thickness biopsy in older children (e.g., toddlers) or adults, particularly if their laboratory relies entirely on H&E-stained sections to exclude HSCR (see below).

Surgeons are taught that a rectal biopsy should be taken 2 cm from the anorectal junction (dentate line) to avoid sampling a zone of physiologic hypoganglionosis (perhaps aganglionosis), which exists in the distal rectum of some otherwise normal infants. The basis for this recommendation dates back to an autopsy study by Aldridge and Campbell [8], which was performed in an era when microscopic identification of ganglion cells in H&E-stained paraffin sections was the only method used to exclude HSCR. Aldridge and Campbell examined H&E-stained sections from postmortem samples of distal rectum for a group of 20 individuals ranging from premature infants to age 15 years. For most of the specimens, ganglion cells were quantified in three representative full-thickness sections, whereas serial sections of biopsy-size sections were only studied for two patients. The serial sections, which were evaluated in a manner most comparable to suction biopsies, demonstrated <1 ganglion cell per mm^2 in the superficial submucosal plexus 1 cm immediately superior to anal mucosa versus ~15 ganglion cells per mm^2 in tissue 2 cm or more proximal to anal mucosa. Although these figures and data from the full-thickness sections clearly demonstrate hypoganglionosis, they are not sufficient to conclude that an adequate suction biopsy from a non-HSCR patient can appear aganglionic with generous histological sampling—sections through the entire block if necessary. In fact, a subsequent autopsy study of punch biopsies taken 0.5–1 cm from anal mucosa from 68 infants and children found ganglion cells (no false positive diagnoses of aganglionosis) in all cases, with a maximum of 25 H&E-stained sections from each biopsy [9]. This has been the author's experience as well, in that suction biopsies obtained "1 cm" from the ani of non-HSCR patients require more sections on average to find a ganglion cell than more rostral biopsies, but invariably contain a definite ganglion cell if adequate submucosa is present and the biopsy is sectioned thoroughly (more than 100 sections in rare cases).

Reluctance to biopsy the distal 2 cm of rectum is a potentially serious issue because even very short-segment aganglionosis, restricted to the distal 1–2 cm, can cause significant morbidity. Suction biopsies are performed transanally in an often distressed infant. The dentate line is not visualized and the relative position of the biopsy instrument's aperture to the dentate line is estimated. It is not uncommon for a biopsy designated "2 cm above the anus" to contain squamous mucosa, indicating operator error of at least 2 cm. It seems equally likely that a biopsy might be one or more centimeter rostral to the intended location, whereby very short segment HSCR might be missed. Our laboratory and many others typically request biopsies from at least three sites (e.g., 1-, 2-, and 3-cm from the anorectal junction) [10]. This practice reduces the likelihood of inadequate sampling due to either a biopsy that is "too low" (squamous or transitional mucosa) or insufficient submucosa, and affords an opportunity to evaluate innervation of the distalmost rectum. When adequate submucosa is sampled and the biopsy is sectioned thoroughly, it is almost always possible to confidently diagnose or exclude HSCR with this approach, particularly if coupled with one or more of the ancillary methods discussed below.

The histopathological hallmarks of aganglionosis are absence of ganglion cells and hypertrophic submucosal nerves (Fig. 17.1). Hypertrophic nerves represent an increased density and caliber of cholinergic nerves that ramify through the bowel wall in the absence of intrinsic enteric neurons. Hypertrophic nerves originate from autonomic and possibly sensory ganglion cells outside the bowel wall, which enter from the mesentery and normally make up a small portion of the nerves in the enteric plexuses. Like other extra-enteric peripheral nerves, they are enclosed by perineurial cells, which express glucose transporter 1 (Glut1) (Fig. 17.1c). In aganglionic submucosa many large nerves are usually conspicuous, particularly in the distal rectum. Monforte-Munoz et al. measured the diameters of submucosal nerves in aganglionic biopsies from 20 patients with HSCR and compared them with 50 ganglionic control biopsies [11]. They reported that control nerves were never more than 40 μm thick, whereas 90 % of biopsies from HSCR patients contained one or more biopsy >40 μm in caliber. This "40 μm rule" is a helpful guideline, but should not be relied on too strongly, particularly with older patients. Nerve caliber and density increase with age, and the ages of the controls in the Monforte-Munoz et al. study were not stated. In the author's experience biopsies from toddlers and older children often contain submucosal nerves >40 μm in diameter, particularly full-thickness biopsies, which include deep submucosa. Nonetheless, an experienced pathologist can usually appreciate an age-adjusted overall increase in nerve diameters and density of large nerves, which serves as the most reliable gauge of abnormal extrinsic submucosal innervation in HSCR.

The diagnosis of HSCR is firmly established when a distal rectal biopsy with adequate submucosa shows aganglionosis and unequivocal nerve hypertrophy. However, most honest pathologists will admit to some degree of nervousness rendering a diagnosis based solely on the H&E findings in some cases. Reasons for consternation are many. Nerve hypertrophy is not a consistent finding and the distinction between adequate and inadequate submucosal sampling is arbitrary. Ganglion cells, particularly the immature ones found normally in neonates, can be difficult to distinguish from reactive endothelial cells or lymphocytes. Inflammation, not uncommon in the setting of a constipated infant who has

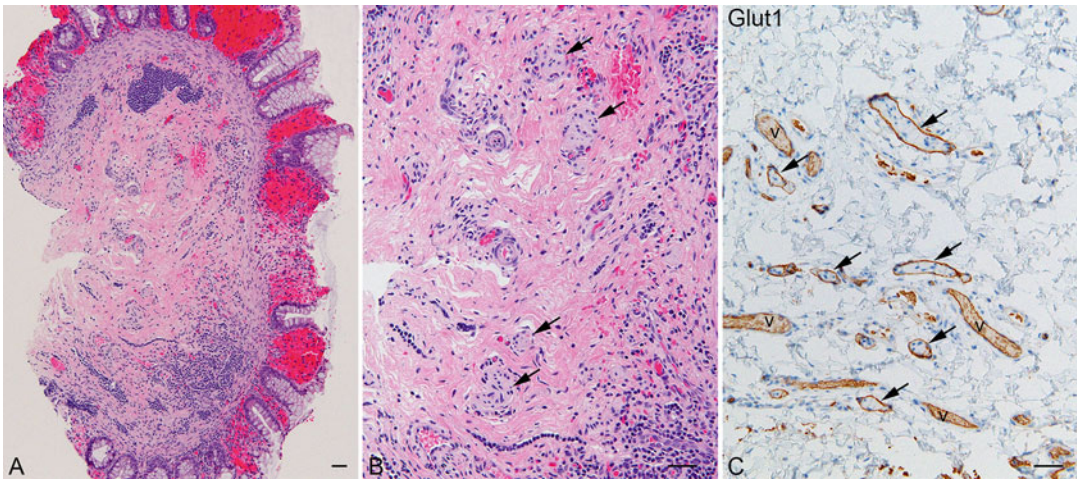

Fig. 17.1 Diagnosis of Hirschsprung disease by rectal suction biopsy. (**a**) An adequate suction rectal biopsy should be ≥2 mm in greatest dimension and contain a generous sample of submucosa. (**b**) Hirschsprung disease is diagnosed based on absence of ganglion cells in exhaustive histological sections of an adequate biopsy and the presence of crowded abnormally large caliber submucosal nerves (*arrows*). (**c**) Hypertrophic submucosal nerves (*arrows*) have Glut1-immunoreactive perineuria similar to extra-enteric (extrinsic) nerves. Glut1 also labels erythrocytes in vessels (v). Scale bars = 40 μm

undergone rectal examination, barium enema, and possibly other diagnostic procedures, can obscure ganglion cells. The diagnostic challenge is compounded by artifacts like compression or tissue dessication, which compromise histological resolution. Some of these problems are reduced by careful handling and expedient transportation/fixation. Unless enzyme histochemistry (see below) is planned, biopsies can be fixed at the bedside and sent to the laboratory in fixative. Any unfixed biopsies should be sent to the laboratory in a sealed container on a saline-moistened telfa pad and promptly fixed or frozen by laboratory staff.

The many challenges working with H&E-stained sections have led to many proposed ancillary histopathological approaches to evaluate rectal biopsies. Several papers have been published which tout immunohistochemistry to detect neuronal markers (e.g., PGP9.5) to facilitate recognition of ganglion cells [12], but very few laboratories employ these methods because in most cases ganglion cells, when present are fairly abundant and readily identified by H&E staining. When ganglion cells are rare, finding them requires evaluation of many sections from a given biopsy, which would require immunostains on an impractically large number of sections and/or destaining and immunostaining H&E sections with equivocal ganglion cells. In contrast, two widely utilized ancillary approaches, acetylcholinesterase (AChE) histochemistry and calretinin immunohistochemistry, detect changes in mucosal innervation which complement information gleaned from H&E sections.

Use of AChE histochemistry as a diagnostic tool for HSCR was pioneered by Meier-Ruge in the 1970s [13]. AChE is expressed on the membranes of cholinergic nerves from pelvic autonomic ganglia, which enter the distal rectum and project rostrally through all layers of the bowel wall. In the normal mucosa, these nerves are slender and sparse (Fig. 17.2a). However, in aganglionic rectum mucosal AChE-positive nerves are thick and concentrated (Fig. 17.2b) [14]. In experienced laboratories, AChE immunostaining alone appears to be a fairly sensitive and specific diagnostic approach [15, 16]. However, performance and interpretation of AChE histochemistry requires regular practice. False negative results from biopsies of premature infants or term babies less than 3 weeks of age are particularly problematic because, as with submucosal nerve hypertrophy, the density, coarseness, and extent of mucosal AChE-positive innervation increase with age [16, 17].

Multiple factors restrict use of AChE histochemistry to specific centers. Some practices, particularly those with small pediatric volumes, cannot justify the expense and effort required to maintain a histochemical assay that is used relatively infrequently. AChE histochemistry also necessitates frozen tissue, typically an additional suction biopsy, because the enzymatic activity is lost when tissues are formalin-fixed and embedded in paraffin. Acquisition of additional tissue and appropriate handling can be impediments, especially if biopsies are performed in remote clinics.

Calretinin immunohistochemistry is another ancillary method to resolve changes in mucosal innervation that correlate with aganglionosis, and has been adopted by many laboratories as an alternative or complement to AChE histochemistry. Calretinin is a calcium-binding protein expressed in a subset of submucosal and myenteric ganglion cells, including muscularis mucosae and lamina propria neurites from intrinsic neurons (Fig. 17.2c) [18]. Aganglionic bowel is devoid of calretinin-immunoreactive mucosal innervation

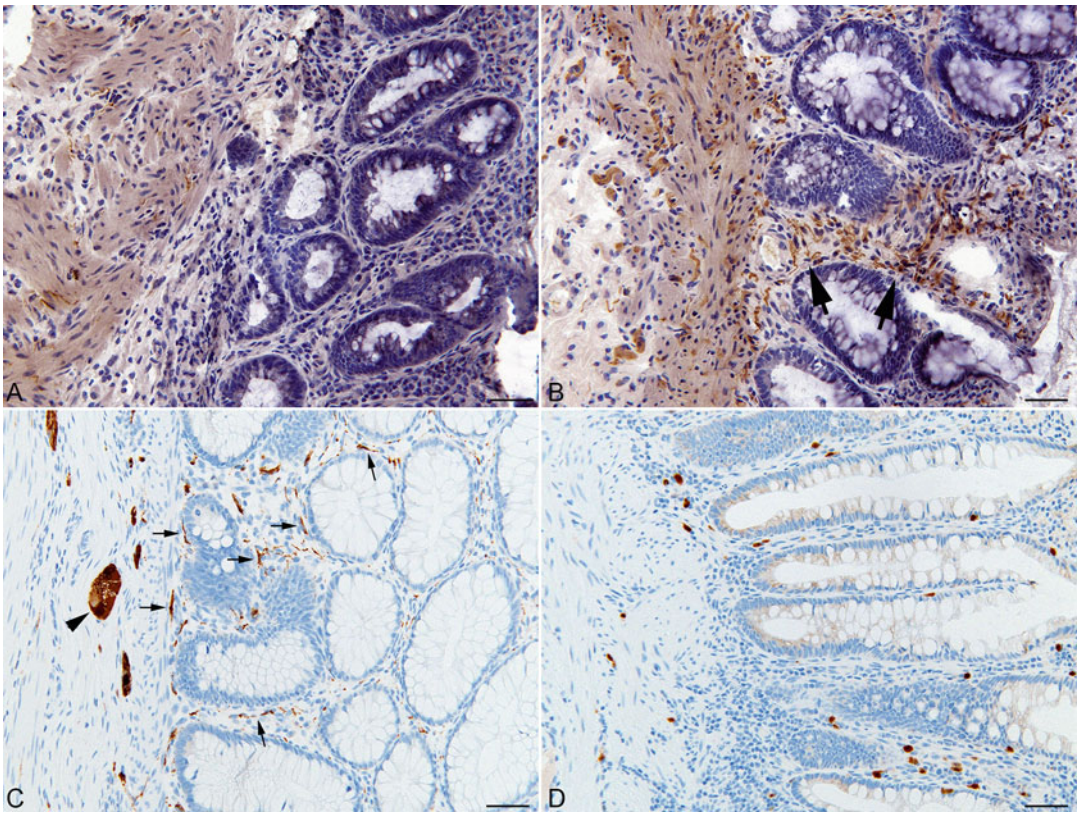

Fig. 17.2 Ancillary staining methods for Hirschsprung disease. (**a**, **b**) Acetylcholinesterase histochemistry highlights cholinergic nerve twigs which are sparse in normal mucosa (**a**) but abundant (*arrows*) in the mucosa overlying aganglionic rectal tissue. (**c**, **d**) Calretinin-immunoreactive ganglion cells (*arrowhead*) and mucosal neurites (*arrows*) are present in a biopsy of ganglionic rectum (**c**) but absent in mucosa overlying aganglionic rectal tissue (**d**). Round immunoreactive structures in (**d**) are mast cells. Scale bars: 50 μm

(Fig. 17.2d), except in a 1–2 cm region immediately distal to ganglionic bowel, where neurites from the latter extend into the mucosa of the aganglionic segment [19]. Calretinin immunohistochemistry can be performed on formalin-fixed paraffin-embedded sections, so no additional biopsies or special tissue processing is required. More importantly, several studies have demonstrated equivalent or superior diagnostic specificity and sensitivity to AChE histochemistry [20–22], although rare situations exist when calretinin immunohistochemistry may be misleading (e.g., very short-segment aganglionosis) [19, 23].

"Full-Thickness" Rectal Biopsy

Full-thickness biopsies require anesthesia and may be associated with slightly higher rate of complications that suction biopsies, but are indicated in certain situations. One frequent use is to exclude HSCR in a toddler or older patient, particularly if prior suction biopsies yielded inadequate submucosa. Other indications for full-thickness biopsy include results from suction biopsies that suggest possible very short-segment HSCR and evaluation of a patient with chronic obstructive symptoms months to years after HSCR surgery to exclude transition zone pull through. Since full-thickness biopsies are performed under anesthesia, the surgeon is able to visualize the anorectal transition and any prior surgical anastomosis boundary and establish the exact location of the biopsy. Whether truly full-thickness or not, any longitudinal incisional biopsy should be oriented by the surgeon to designate the proximal and distal ends because a transition between ganglionic and aganglionic bowel may be evident along the length of a 2–4-cm-long "strip" biopsy and provide definitive evidence for very short segment HSCR. In a patient, whose obstructive symptoms persist long after a pull-through procedure, punch biopsies taken at four quadrants just proximal to the anastomosis line may be used to exclude features of transition zone pull through (e.g., partial circumferential aganglionosis, hypoganglionosis, or nerve hypertrophy), which may involve only portions of the bowel circumference [24–26]. Most full-thickness biopsies are large enough to be divided and freeze a small portion including mucosa and submucosa for histochemical staining, if indicated.

Diagnosis of Intestinal Neuronal Dysplasia by Rectal Biopsy

Rectal biopsy is the principal diagnostic procedure for isolated intestinal neuronal dysplasia type B (IND). IND was first described by Meier-Ruge in patients with symptoms of Hirschsprung disease but ganglion cells in their rectal biopsies [27]. The diagnostic criteria have evolved with time, but remain based on counts of submucosal ganglion cells, as identified by enzymatic histochemical staining for lactate dehydrogenase and/or succinate dehydrogenase activities [28]. The latter, like AChE histochemistry, are performed on frozen sections, but the quantitative analysis requires a standardized section thickness (15 μm) and is subject to significant observer bias [29]. Formalin-fixed paraffin-embedded biopsies are not adequate. An overabundance of "giant" submucosal ganglia (>8 ganglion cells/ganglion in an appropriately stained section) is the primary diagnostic feature of IND. However, the proportion of giant ganglia appears to change with age [30], and the formal diagnostic criteria are not considered valid for patients under a year of age [28].

IND has also been reported in ganglionic bowel proximal to the aganglionic segment in HSCR, albeit mostly in patients less than a year of age, a finding that some studies suggest may portend a worse outcome after pull-through surgery [31–37]. Recently, we used paraffin sections, immunostaining for the neural marker Hu C/D, and colonic tissue from autopsy control infants (no history of dysmotility) to establish diagnostic criteria for IND-like submucosal hyperganglionosis (IND-SH) [38]. Based on these criteria, IND-SH (deviations >3 standard deviations from controls) were observed at the proximal surgical margin of 15 % of patients with short-segment HSCR, up to 15 cm proximal to the aganglionic segment.

Considerable confusion and controversy exists regarding IND. Many have questioned the existence or clinical significance of this histopathological phenotype [30, 39–43]. Skepticism is due to many factors including lack of appropriate controls, changes in diagnostic criteria, erroneous extrapolation of diagnostic criteria to H&E-stained paraffin sections, and claims increased abundance of giant submucosal ganglia is a secondary adaptation to downstream obstruction, as opposed to a primary neuropathy. At this time, it seems prudent to regard IND as an "investigational" phenotype in need of research studies with appropriate controls to validate diagnostic features and demonstrate any clinical significance. Certainly the diagnosis should not be rendered based solely on analysis of paraffin sections or outside the context of a reference laboratory, which has performed adequate internal validation studies.

Use of Rectal Biopsies to Diagnose Other Conditions

Rectal biopsy is primarily a procedure to diagnose HSCR or IND, and the deliberate search for other histopathologic etiologies for intestinal dysmotility is best approached with full-thickness or seromuscular biopsies from other parts of the gastrointestinal tract. Suction biopsies and many biopsies designated as "full-thickness" by the surgeon fail to extend into the muscularis propria, and provide no insight into the muscularis propria or myenteric plexus. Those that truly are full-thickness generally sample a very small portion of the muscularis propria and myenteric plexus. Small sample size and the normal hypoganglionic nature of the distal rectum prohibit diagnosis of hypoganglionosis and reduce the likelihood of recognizing key pathological features that are only present in a small subset of neurons or muscle cells (e.g., inclusion disorders). Furthermore, the neuromuscular microanatomy of the distal rectum is different from most of the rest of the intestines and mimics changes considered pathologic in other sites. The muscularis propria of the distal rectum is thickened and separated into discrete bundles by fibrous tissue, which also interdigitates between the muscularis externa and interna around the myenteric plexus. Elsewhere this pattern of fibrosis might suggest visceral myopathy or post-inflammatory scarring. As discussed above, except in infants and young toddlers, large submucosal nerves with extrinsic morphological features (e.g., conspicuous Glut1-immunoreactive perineurium) are normal in the distal rectum, but not more proximally. These nerves are identical in size to, but fewer in number than, the large caliber nerves observed in the transition zone of HSCR. In an infant with HSCR they are regarded by many as an indicator of physiologically abnormal bowel that can cause persistent obstructive symptoms if it is not resected during a pull-through procedure [44, 45]. In the distal rectum of an older patient, occasional large nerves are normal and aganglionosis or prior transition zone pull through should only be suspected if abundant large nerves are present.

Despite these potentially misleading features, occasionally findings in a rectal biopsy done to exclude HSCR actually lead to another specific diagnosis. While insensitive, rectal biopsy has led to accurate diagnosis of conditions associated with inclusions in ganglion cells such as mitochondrial disorders [46, 47] or neuronal nuclear inclusion disease [48]. In principle, diagnostic features of some inflammatory visceral myopathies or neuropathies might also be evident in a true full-thickness rectal biopsy, which samples a generous amount of muscularis propria and myenteric plexus. Although widespread involvement of the intestinal tract is usually present in these very rare disorders, the changes can be patchy and we have no idea how often rectal

tissues are affected. More typically multiple sizable laparoscopic or open surgical intestinal biopsies are considered the diagnostic standard for adequate evaluation.

Intestinal Biopsy to Evaluate a Patient with Chronic Pseudo-obstruction

Once HSCR is excluded, most infants either resolve their symptoms or can be managed satisfactorily with dietary/medical therapy. Unfortunately other patients continue to have debilitating dysmotility or acquire chronic intestinal pseudo-obstruction as older children or adults. Clinical findings in many of these patients are difficult to distinguish from true obstruction, and it is not uncommon for them to undergo laparotomy to exclude an anatomic etiology. After anatomic cause is excluded, the recurrent nature of their disorder coupled with a history of prior abdominal exploration prompts concerns about obstruction due to abdominal adhesions, which can lead to multiple laparotomies in some instances. Diversion enterostomy is also a common, particularly for those patients with profound colonic dysmotility. Intestinal biopsy is often considered as part of any of these surgeries or sometimes as a primary diagnostic procedure. Intestinal biopsy to identify ganglionic bowel for either a leveling ostomy or primary pull-through procedure is also an integral component of HSCR management.

Diagnostic intestinal biopsies from patients with intestinal pseudo-obstruction are performed cognizant that (a) similar clinical findings may be due to numerous etiologies, not all of which have anatomic correlates, (b) diagnostic histopathological features are often patchy and may be missed with inadequate or unlucky sampling, (c) key histological findings can be mimicked or obscured by artifacts associated with improper handling, and (d) many diagnoses have prognostic or genetic implications, but will not significantly affect clinical management. No standard exists with regard to which or how many sites should be biopsied from a patient with pseudo-obstruction. Sometimes manometric data or other clinical findings suggest more severe involvement of one part of the intestinal tract. However, it is prudent to biopsy multiple sites including large and small intestine to gain information about the distribution of pathological changes and their severity/progression. If segmental dilatation is present, at least one biopsy should be from the dilated area and another from bowel immediately downstream.

An international working group recommended full-thickness biopsies at least 1.5 × 1.5 cm, with transverse closure of the surgical defect [49]. In my experience with pediatric patients, biopsies are more often rectangular or ovoid, range from 1 to 1.5 cm in greatest dimension, and provide adequate tissue for evaluation. Priority should be given to obtaining well-oriented, undamaged, formalin-fixed, paraffin-embedded tissue sections. However, it is usually possible to save a 1 mm^3 sample of muscularis propria and enclosed myenteric plexus in electron microscopy fixative and snap freeze small full-thickness portions of each biopsy. Pre-surgical coordination between pathologist and surgeon is advisable and the surgeon should procure biopsies with gentle traction (typically applied with a nylon suture) and send the specimen to the laboratory for immediate processing. Orientation of the biopsy so that sections are cut perpendicular to the serosal surface is most important, and a biopsy should ideally be aligned in a true transverse or longitudinal plane.

As with rectal biopsies, H&E-stained sections provide the starting point for histological evaluation of intestinal biopsies. Generally a single slide (1–3 sections per slide) is sufficient; additional sections or special stains are obtained as needed. Trichrome-stained sections provide good contrast between smooth muscle and collagen-rich fibrous tissue, and are often helpful to resolve intramuscular fibrosis. Except as a research tool, immunohistochemistry should be guided by the clinical and H&E findings. Immunohistochemistry can help identify and quantify specific cell types (e.g., neurons, enteric glia, interstitial cells of Cajal, fibroblast-like cells, and smooth muscle) involved in enteric neuromuscular activity, and has been used to distinguish specific subtypes of enteric neurons and/or the distribution of their cell processes. However, for the most part, disease-specific alterations in the density, distribution, or intensity of immunoreactive cells have not been found.

For example, consider CD117 (c-kit) immunohistochemistry. In the gut wall, CD117 is a fairly specific marker for interstitial cells of Cajal (mast cells also express this antigen), which mediate intestinal pacemaker activity. However, CD117-positive interstitial cells are difficult to quantify, especially in tissue sections. Reduced or absent CD117-immunoreactive pacemaker cells have been reported inconsistently in multiple contexts, including diverse conditions (e.g., HSCR, post-inflammatory strictures), as what appears to be a nonspecific secondary change [50, 51]. Nonetheless, many pathologists use CD117 immunochemistry in their work-up of intestinal biopsies from patients with pseudo-obstruction, with no clear idea how results of such analysis should be interpreted. Similarly, poorly understood alterations in the densities of neurochemically defined subtypes of enteric neurons have been reported in patients with slow transit constipation, hypoganglionosis, idiopathic megacolon, transition zone of Hirschsprung disease, and congenital chronic intestinal pseudo-obstruction [52].

Additional Disorders Diagnosed by Biopsy

Some types of intestinal neuropathology that can be diagnosed from biopsies are listed in Table 17.1 and their histopathological features are briefly reviewed in the following sections.

Table 17.1 Intestinal neuromuscular pathology in intestinal biopsies

Diagnosis[a]	H&E findings	Ancillary pathology	Confirmatory studies
Congenital hypoganglionosis	Sparse myenteric ganglion cells organized as individual cells or pairs with minimal adjacent neuropil	May require multiple levels to confirm impression and determine extent of intestinal involvement; immunohistochemistry with neuronal markers (e.g., Hu C/D, PGP9.5) may help resolve ganglion cells	None (genetic basis unknown)
Degenerative enteric neuropathy (including inflammatory neuropathies)	Reduced density of ganglion cells without significant loss of adjacent neuropil; degenerating neurons; lymphocytic or eosinophilic ganglionitis; rarely neuronal nuclear inclusion disease	Immunohistochemistry to document intra-ganglionic T-cells; consider electron microscopy or immunohistochemistry to characterize intranuclear inclusions	Serology for anti-neuronal antibodies
Ganglioneuromatosis/Neurofibromatosis	Ganglioneuromatous or neurofibromatous hyperplasia of enteric plexuses with or without mucosal neuromas		Other clinical features; *RET* (MEN2B), *NF1*, or *PTEN* (Cowden) mutational analysis
Mitochondrial disorders	Eosinophilic cytoplasmic inclusions (megamitochondria) in ganglion cells; atrophy of muscularis externa	Electron microscopy to document megamitochondria +/− abnormal cristae	Other clinical features; Reduced plasma thymidine phosphorylase activity in MNGIE; Mutational analysis for various established hereditary mitochondriopathies (e.g., Alpers, MNGIE)
Diffuse abnormal layering of small intestinal smooth muscle	Markedly disorganized lamination of muscularis propria (e.g., trilaminar)	Immunohistochemical demonstration of absent Filamin A	Other clinical features: *FLNA* mutational analysis
Megacystis microcolon intestinal hypoperistalsis syndrome	No consistent histopathological alterations	Possibly abnormal "clumping" of actin-gamma-2 in smooth muscle cells	*ACTG2* or *MYH11* mutational analysis
Familial visceral myopathy	No consistent histopathological alterations; fibrosis and myocyte vacuolar degeneration are common, but patchy	Possibly abnormal "clumping" of actin-gamma-2 in smooth muscle cells	*ACTG2* or *MYH11* mutational analysis[b]
Inflammatory myopathies (visceral leiomyositis)	Dense and usually diffuse lymphocytic or eosinophilic inflammation of muscularis propria	Immunohistochemistry to document intra-ganglionic T-cells	Serology to demonstrate anti-smooth muscle antibodies

[a]Based in part on the London Classification of gastrointestinal neuromuscular pathology [52]: clinical-histopathologic correlates with established etiologies as determined by consensus of an International Working Group. Excludes morphological abnormalities that may be clearly identifiable, but provide only weak evidence of the pathogenic mechanism and may not be causally related to an observed clinical entity

[b]FVM has heterogeneous etiologies and *ACTG2* or *MYH11* mutations are found in only a subset, including many with only nonspecific or negative histopathological findings

Congenital Hypoganglionosis

"Hypoganglionosis" denotes a reduced density of neurons relative to normal. In a literal sense, the term encompasses a wide range of possible abnormalities, including relatively small alterations in neuronal number and/or loss of selective subtypes of neurons. Even in resection specimens, such small changes are impossible to diagnose by simple analysis of H&E-stained sections and very difficult to diagnose reliably even with immunostaining and/or sophisticated types of morphometric analysis. The problem is compounded by the limited sample present in a typical intestinal biopsy, marked variation in the observed numbers of ganglion cells observed in control populations [26, 53], and uncertainty about how distension may affect ganglion cell density. For this reason, many of us only express confidence recognizing moderate-to-severe myenteric hypoganglionosis (to the best of my knowledge, submucosal hypoganglionosis per se has not been described). Myenteric hypoganglionosis can be congenital ("hypogenesis") or acquired. Acquired forms are neurodegenerative conditions and described in the next section.

The severe and readily recognized form of congenital hypoganglionosis can be diagnosed in H&E-stained sections, provided a generous biopsy of at least one-fourth of the bowel wall circumference is obtained. The essential microscopic features are a predominance of small myenteric ganglia (one or two ganglion cells) with minimal amounts of surrounding neuropil (Fig. 17.3) [54]. Because the entire myenteric plexus is hypoplastic, the laminae of the muscularis propria are closely apposed and ganglion cells are tightly sandwiched between the two muscle layers. Ganglion cell size and cytology may be normal or relatively immature. Submucosal ganglia are usually not affected, and their density often appears to exceed that of myenteric ganglia. Immunostains are not necessary, but neural markers may help resolve immature ganglion cells and exclude aganglionosis. Reduced AChE-positive innervation has been touted as a helpful diagnostic feature, and many published studies of hypoganglionosis are from laboratories that use this technique routinely [55]. Diffuse involvement of the intestinal tract is typical, but similar features may be observed in the transition zone of HSCR. In the transition zone, particularly in short-segment HSCR, hypertrophic extrinsic nerves coexist with hypoganglionosis, whereas hypertrophic myenteric or submucosal nerves are not part of isolated congenital hypoganglionosis. The pathogenesis of congenital hypoganglionosis is unknown, but does not appear to overlap genetically with HSCR [56].

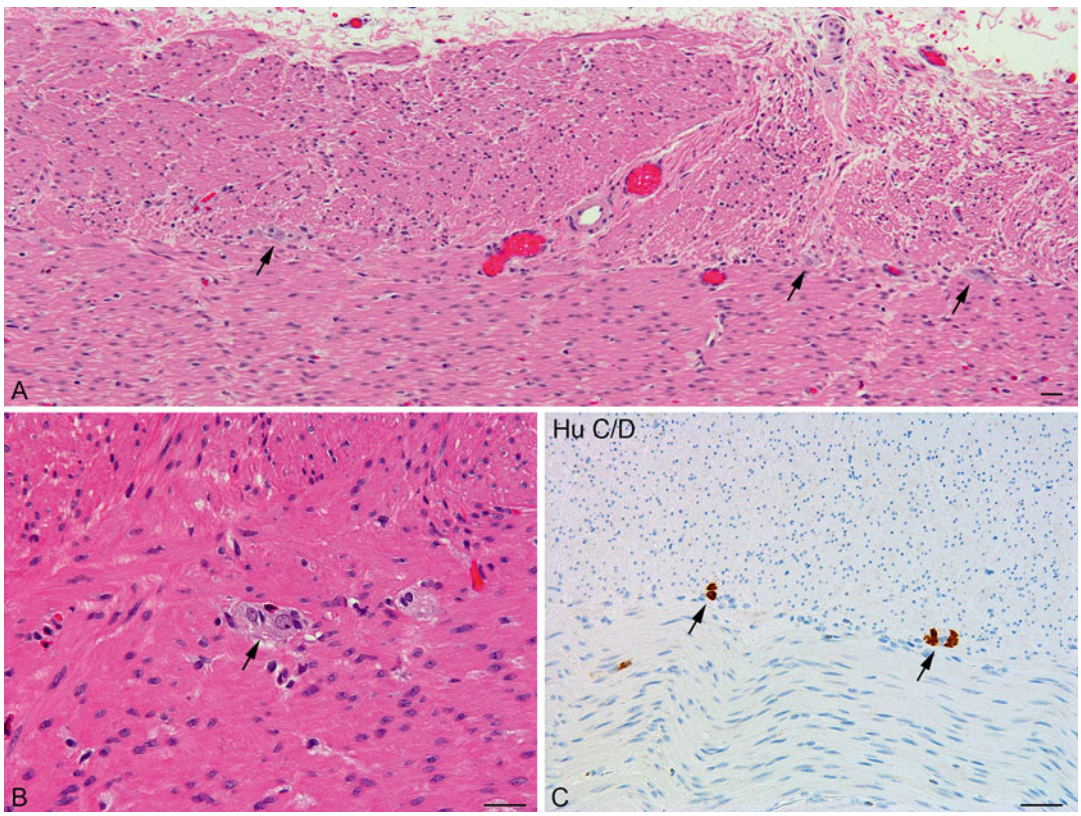

Fig. 17.3 Hypoganglionosis. (**a**) At low magnification, a "string" of very small myenteric ganglia (*arrows*) is found at the interface between the muscularis interna and externa. (**b**) Each small ganglion (*arrow*) is composed of one or two neurons with minimal neuropil. (**c**) Hu C/D immunostain highlights the sparse myenteric ganglion cell bodies. Scale bars: 50 μm

Ganglioneuromatosis/Neurofibromatosis

Dysmotility due to hyperplasia and disorganization of enteric nervous system components is recognized as part of the phenotypic spectrum of at least three hamartoma syndromes—multiple endocrine neoplasia type 2B (MEN2B), neurofibromatosis type I (NF1), and Cowden syndrome [57]. Ganglioneuromatous hyperplasia can occur with any of the three conditions, whereas intestinal neurofibromas are only associated with NF1. These lesions can occur anywhere along the length of the bowel and involve mucosa, submucosa, or myenteric plexus, although pseudo-obstruction is most often associated with diffuse lesions that involve extramucosal portions of the bowel wall. Ganglioneuromatous enteric lesions have been subdivided into diffuse ganglioneuromas, ganglioneuromatous polyposis, and solitary polypoid ganglioneuroma [58]. Diffuse ganglioneuromas are composed of variable numbers of ganglion cells, glial cells, and nerve processes, and have an infiltrative growth pattern, frequently along exaggerated neural pathways in the myenteric, intramuscular, and submucosal plexuses (Fig. 17.4a–c). Diffuse ganglioneuromas are almost invariably syndromic, and often associated with similar mucosal hamartomas (Fig. 17.4d, e), but mucosal lesions alone do not necessarily imply a syndrome. Solitary polypoid ganglioneuroma is a sporadic mucosal hamartomatous lesion, which only produces dysmotility due to anatomic obstruction or intussusception. Polypoid ganglioneuromas are formed by collections of cytologically mature ganglion cells, glia, and neuropil in the lamina propria, which displace adjacent crypts or glands. The presence of many such lesions constitutes ganglioneuromatous polyposis. A syndromic basis for at least some examples of ganglioneuromatous polyposis has been suggested, but no definite syndrome or genetic association has been identified [57]. While the ganglion cells of these hamartomas are easy to recognize, the network of neural tissue that accompanies them may be difficult to distinguish from surrounding lamina propria or smooth muscle. S100 immunostain highlights the nerve processes and associated glial cells.

Mitochondrial Disorders

Intestinal pseudo-obstruction is a frequent, sometimes severe, and occasionally initial problem for patients with hereditary mitochondrial disease. For patients with severe enteric manifestations, in addition to central nervous system pathology, the term mitochondrial neurogastrointestinal encephalomyelopathy (MNGIE) is used. Similar gastrointestinal dysfunction and pathological findings have been described in patients with mutations in at least three different genes [59], including patients with *POLG1* mutations and Alpers syndrome [47]. Histopathological features of mitochondriopathy are multifocal thinning or loss of the muscularis externa and megamitochondria in enteric neurons +/– smooth muscle (Fig. 17.5). In H&E-stained sections megamitochondria are dense, eosinophilic cytoplasmic granules 1–5 μm in diameter. They are only observed in a minority of ganglion cells, sometimes less than 10%. Less frequently they can be resolved in smooth muscle cells. Electron microscopy can help clarify that these inclusions are giant mitochondria and sometimes resolves abnormal cristae. A thorough neurological examination and other laboratory tests may reveal extra-enteric findings that help confirm the diagnosis.

Diffuse Abnormal Layering of Small Intestinal Smooth Muscle (X-Linked Pseudo-obstruction)

An X-linked form of familial intestinal pseudo-obstruction was recognized several decades ago and recently shown to be caused by mutations in the Filamin A gene (*FLNA*) [60, 61]. Affected males usually have one or more other congenital anomaly (e.g., cerebral periventricular heterotopias, atrial septal defect, cleft palate) and some are thrombocytopenic. All patients have intestinal malrotation and congenital short small bowel (CSSB). Alterations in the density and relative numbers of argyrophilic and argyrophobic ganglion cells have been described, albeit inconsistently, and led to the impression that the disorder is a primary neuropathy [62]. However, stronger evidence now exists for a primary myopathic basis [63]. *FLNA* is expressed in intestinal smooth muscle, not neurons, and expression is lost in males with *FLNA* mutations and pseudo-obstruction. Histologic sections of well-oriented biopsies demonstrate diffuse foci of disorganized lamination of the small intestinal muscularis propria, including trilaminar architecture (Fig. 17.6). Colonic biopsies from a teen patient showed a unique pattern of myocyte multinucleation in the innermost layers of the muscularis interna [63]. Although abnormal layering has been observed throughout the small intestine in those few cases with extensive sampling, intact lamination is present in some areas and diagnostic features could be missed with a small biopsy. Therefore, immunohistochemistry and/or mutational analysis should be considered for a male patient with CSSB.

CSSB and intestinal malrotation also result from recessive mutations in the autosomal gene, Coxsackie and adenovirus-receptor like membrane protein (*CLMP*) [64]. However, neither pseudo-obstruction nor abnormal smooth muscle lamination is part of the phenotype in *CLMP*-related CSSB.

Degenerative Enteric Neuropathy

The London classification system for gastrointestinal neuromuscular pathology recognizes neuronal degeneration with or without associated inflammation of ganglia as an etiology for

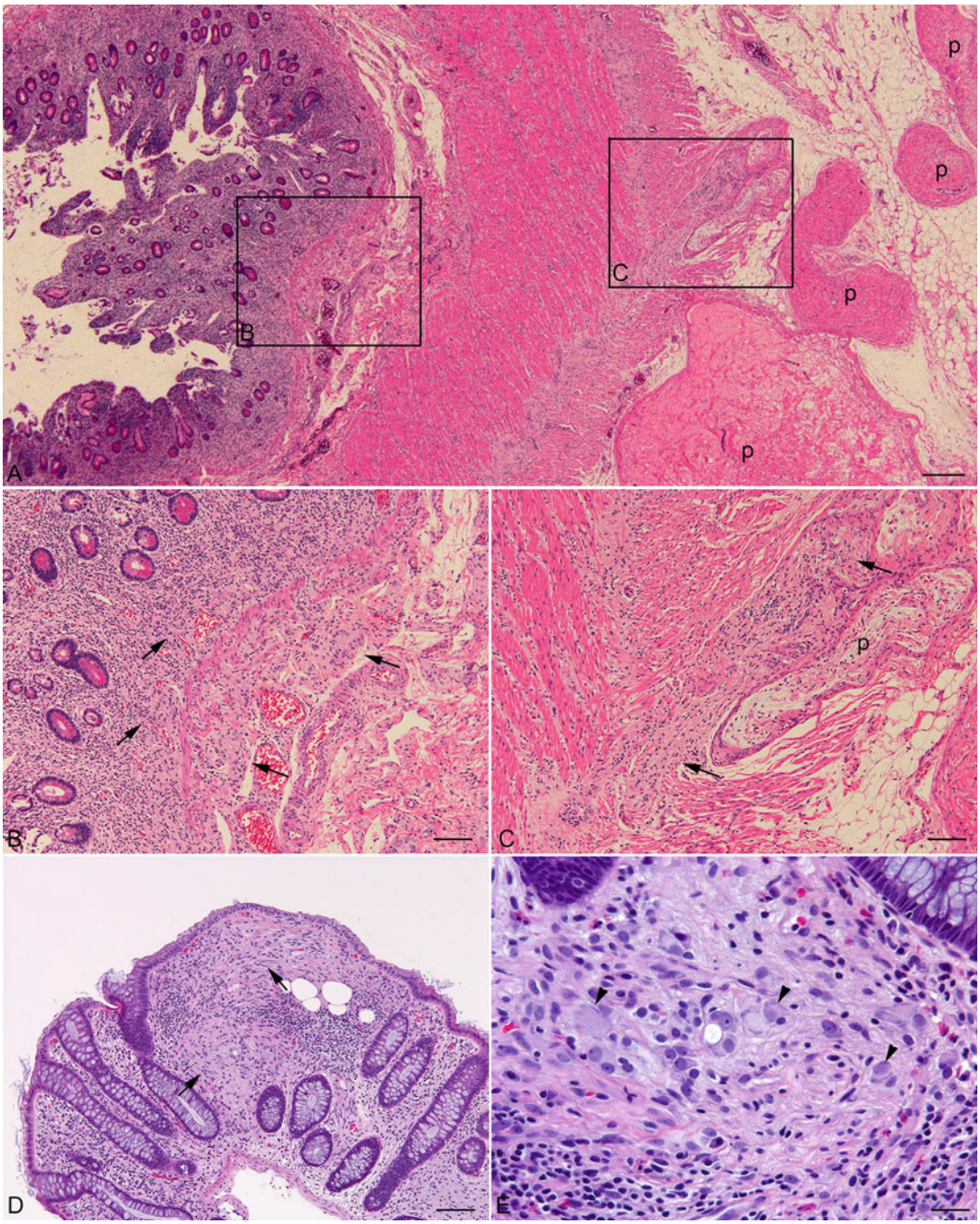

Fig. 17.4 Ganglioneuromatous hyperplasia (neurofibromatosis and multiple endocrine neoplasia type 2B). (**a**) Low magnification image shows a plexiform neurofibroma in the mesentery of the small bowel in a patient with neurofibromatosis. Ganglioneuromatous hyperplasia (*arrows*) is present in the underlying myenteric plexus (**b**) and submucosa/mucosa (**c**). (**d**, **e**) A mucosal ganglioneuroma (*arrows*) in a patient with multiple endocrine neoplasia type 2B is composed of ganglion cell bodies (*arrowheads*) and surrounding neuropil. Scale bars: (**a**) 250 μm; (**b**) 100 μm; (**c**) 100 μm; (**d**) 100; (**e**) 25 μm

intestinal pseudo-obstruction [52]. Recognition of neuronal degeneration is subjective, and one should be wary about a diagnosis based on subtle cytological changes like nuclear condensation, cytoplasmic hypereosinophilia, cellular vacuolization, or irregular cell contours. Unequivocal forms of neuronal degeneration are associated with one or more of the following: moderate-to-severe hypoganglionosis, lymphocytic or eosinophilic ganglionitis, pathological intranuclear or cytoplasmic inclusions, and nuclear pyknosis or fragmentation. Although inflammatory cells often cluster in the periganglionic space between the muscularis interna and externa, it is rare to find lymphocytes or eosinophils within ganglia. Even

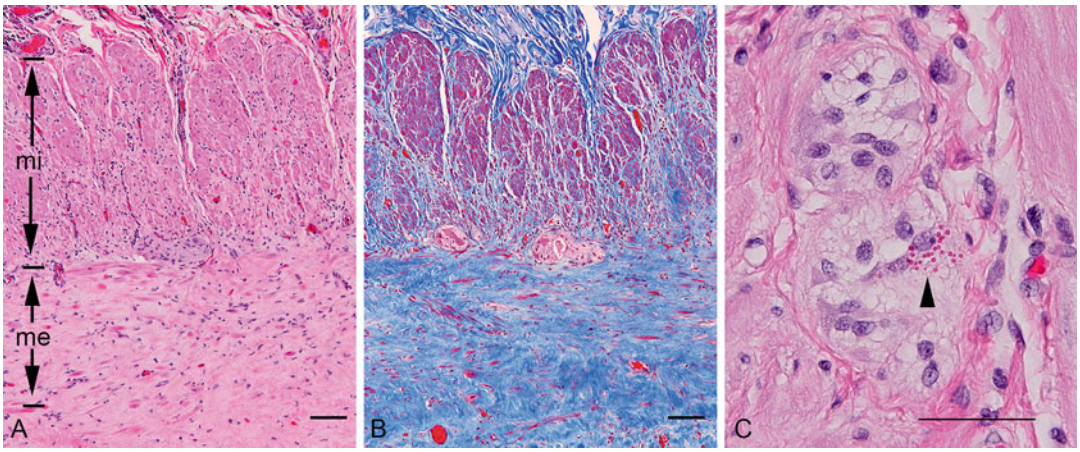

Fig. 17.5 Mitochondriopathic histopathology. (**a**, **b**) H&E- (**a**) and trichrome- (**b**) stained sections show near complete effacement of the muscularis externa (me) by fibrous tissue (*blue* in **b**) with less severe atrophy of the muscularis interna (mi). (**c**) Dense eosinophilic granules (megamitochondria) are present in a subset of enteric ganglion cells (*arrowhead*). Scale bars: (**a**) 100 μm; (**b**) 100 μm; (**c**) 50 μm

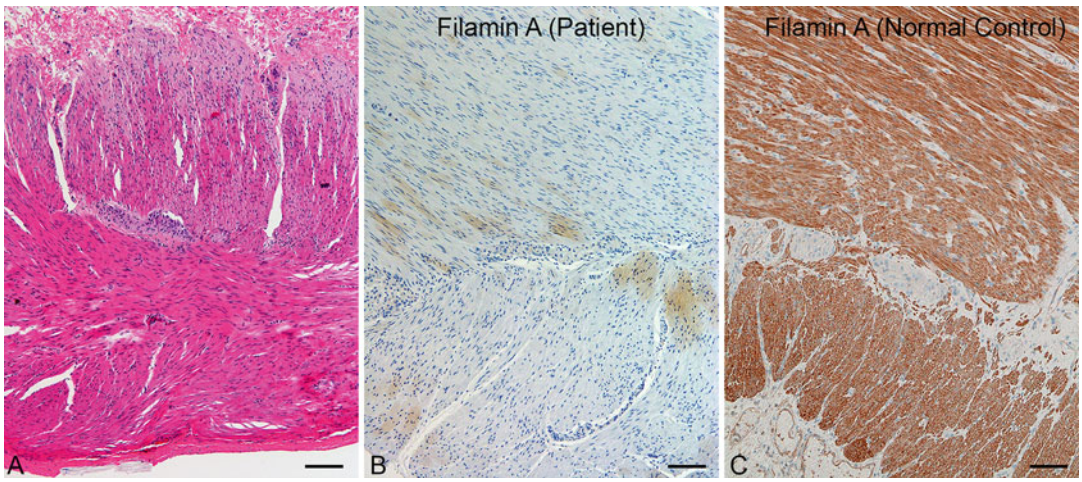

Fig. 17.6 Filamin A-related visceral myopathy (X-linked intestinal pseudo-obstruction). (**a**) H&E-stained section from an area of abnormal lamination in the small intestinal muscularis propria shows a vaguely trilaminar architecture. (**b**) Filamin A immunohistochemistry demonstrates dramatic loss of muscular immunoreactivity, in comparison to the diffuse dense cytoplasmic immunoreactivity in a section of normal control bowel (**c**). Scale bars: 100 μm

in the context of transmural inflammation related to mucosal injury or inflammatory bowel disease, the proportion of inflammatory cells within ganglia is usually small. An exception is in the transition zone of some patients with HSCR, where concentrated intra- or peri-ganglionic eosinophilic inflammation may be present with minimal inflammation elsewhere [65]. As opposed to primary eosinophilic ganglionitis, these HSCR-associated infiltrates are not accompanied by degenerative cytopathology of ganglion cells and are not known to affect neuronal loss, clinical outcome, or motility.

Degeneration of ganglion cells occurs due to varied primary causes, some hereditary (e.g., neuronal nuclear inclusion disease, mitochondrial disorders) and others acquired, is usually progressive, and culminates in hypoganglionosis. Acquired forms include neurodegenerative conditions of the central nervous system like Parkinson disease [66] and inflammatory neuropathies [67]. The pathological findings are widespread, although many individual ganglia are often spared. Extra-enteric findings help narrow the differential diagnosis. Histopathologically, numerous cytotoxic T-cells are present in the ganglia of lymphocytic ganglionitis, without significant inflammation in surrounding smooth muscle. Circulating anti-neuronal antibodies may be identified with lymphocytic ganglionitis, which sometimes arises as a paraneoplastic syndrome in patients with small cell carcinoma or other malignant tumors [68].

Neuronal degeneration and eventual hypoganglionosis are also observed in Chagasic megacolon [69]. Early loss of neu-

rons has been attributed to direct infection by the parasite followed by a chronic phase of lymphocytic ganglionitis and T-cell mediated neuronal apoptosis. Segmental colonic dilatation, as opposed to obvious pan-intestinal dysmotility, is the predominant finding in Chagas disease, and neuronal loss is generally most severe in the dilated segment. The lymphocytic infiltrate can be mild and immunostains for CD3 or other lymphocytic markers may help distinguish lymphocytes from enteric glial nuclei. Alterations in the densities of specific neuronal subsets, enteric glia, and interstitial cells of Cajal have also been reported in Chagasic megacolon, but assessment of these details is not required to make the diagnosis [70].

Hereditary types of intestinal pseudo-obstruction and degenerative enteric neuropathy include some metabolic disorders (e.g., Fabry disease) [71], mitochondrial disorders (discussed above), and neuronal intranuclear inclusion disease [48]. All of these are multisystem disorders that affect the brain and/or other organs, in addition to the bowel. Pathologic nuclear or cytoplasmic change in a subset of ganglion cells is the microscopic key to suspecting each diagnosis (Fig. 17.7). In neuronal intranuclear inclusion disease, hyalinized round inclusions larger than the large nuclei of ganglion cells are present, but even in advanced cases it may require examination of many ganglion cells to find this diagnostic feature. At present, the genetic cause of neuronal intranuclear inclusion disease has not been determined. Infantile, juvenile, and adult forms have been described, and it is possible that the phenotypes correspond to different genetic etiologies. The inclusions contain ubiquitin, SUMO-1 and other proteins found in the nuclear deposits of some "trinucleotide-repeat" disorders, leading to speculation of a mutation in an analogous gene [72]. Electron microscopy demonstrates fine microfibrillar structures easily distinguished from nucleoli or normal chromatin.

Megacystis Microcolon Intestinal Hypoperistalsis Syndrome (MMIHS)

MMIHS is a congenital and severe form of pseudo-obstruction in which intestines and urinary bladder are affected. The bladder and small intestine are distended, but the colon is narrow because propulsion through the small intestine is incomplete. Megacystis may be recognized in utero by prenatal ultrasound examination. The same phenotype likely results from any neural or muscular defected that severely impedes smooth muscle contractility in both organs, and MMIHS probably has multiple etiologies. Familial recurrences and parental consanguinity suggest a hereditary basis for many published cases, and de novo heterozygous mutations in a gene encoding smooth muscle actin (*ACTG2)* or biallelic mutations in myosin heavy chain 11 (*MYH11*) have been documented recently in some patients [73–75].

Despite impressive changes in gross anatomy, the intestinal and bladder histopathology in MMIHS is nonspecific and underwhelming. Past descriptions have alternatively alluded to subtle changes in the enteric nervous system or smooth muscle without clear consensus [76–78]. The most frequent observations have been degeneration and fibrous replacement of smooth muscle and loss of smooth muscle actin immunoreactivity [79–82].

Familial Visceral Myopathy

Familial visceral myopathy (also termed "hollow visceral myopathy") refers to hereditary types of intestinal pseudo-obstruction with or without accompanying urinary bladder, gall bladder, or uterine hypocontractility. An effort has been made to

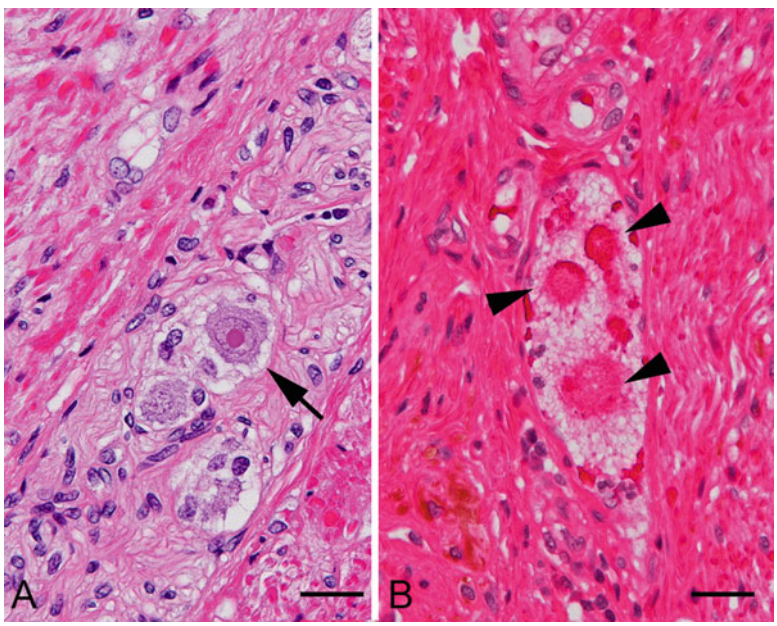

Fig. 17.7 Neuronal intranuclear inclusion disease. (**a**) Large eosinophilic intranuclear inclusions in a subset of neurons (*arrow*) are the diagnostic finding in this condition. (**b**) Rarely acute neuronal degeneration, as evidence by hyper-eosinophilic degenerating ganglion cells (*arrowheads*), is observed. Scale bars: 100 μm

subcategorize familial visceral myopathies based on inheritance patterns (autosomal dominant versus autosomal recessive), age of onset, and clinical-pathological features [83]. However, this scheme has limited clinical utility because of overlap between the groups and nonspecificity of many of the findings. MMIHS is not included in the scheme, but should be considered a severe and early-onset form of familial visceral myopathy, a point made clear by identification of *ACTG2* mutations in children and adults with familial visceral myopathy [84–86].

Histopathological features range from no alterations to severe myocyte degeneration and fibrosis. Degenerating myocytes have condensed, crenated nuclei with perinuclear vacuoles or "halos" [6, 87, 88]. Irregular amounts of collagen accumulate between myocytes and may replace large parts of the muscularis propria. In some cases, one lamina is profoundly affected, but the other is spared. These changes are usually patchy and may be missed with a single biopsy. Inflammation is not a feature of familial visceral myopathy per se. Reduced, absent, or irregular immunostaining for smooth muscle cytoskeletal components (e.g., actin) have been described in some cases [86, 89], but are not a consistent feature. Retention of actin immunoreactivity does not exclude *ACTG2* mutation [84, 85].

Inflammatory Visceral Myopathy (Visceral Leiomyositis)

Inflammatory visceral myopathy exhibits similar myodegeneration and fibrosis to familial visceral myopathy, but in conjunction with inflammation of the muscularis propria. Severe inflammatory visceral myopathy is a rare condition which can affect any age, including young infants. An autoimmune basis is suspected and affected infants often have elevated serum titers of antibodies against smooth muscle actin, although this may be secondary to muscle damage. A dense infiltrate of cytotoxic T-cells (CD3+, CD8+) is present in the muscularis propria and occasionally in the muscularis mucosae (Fig. 17.8) [90, 91]. Vascular smooth muscle is typically spared. The process is diffuse and not likely to be missed with a biopsy.

Although systemic autoimmune disorders (e.g., primary systemic sclerosis) injure enteric muscle and produce dysmotility, inflammation of the bowel wall is usually absent or mild. Fibrosis, likely secondary to vascular injury and secondary muscular ischemia, predominates without myocyte vacuolar degeneration [6]. Other forms of inflammatory

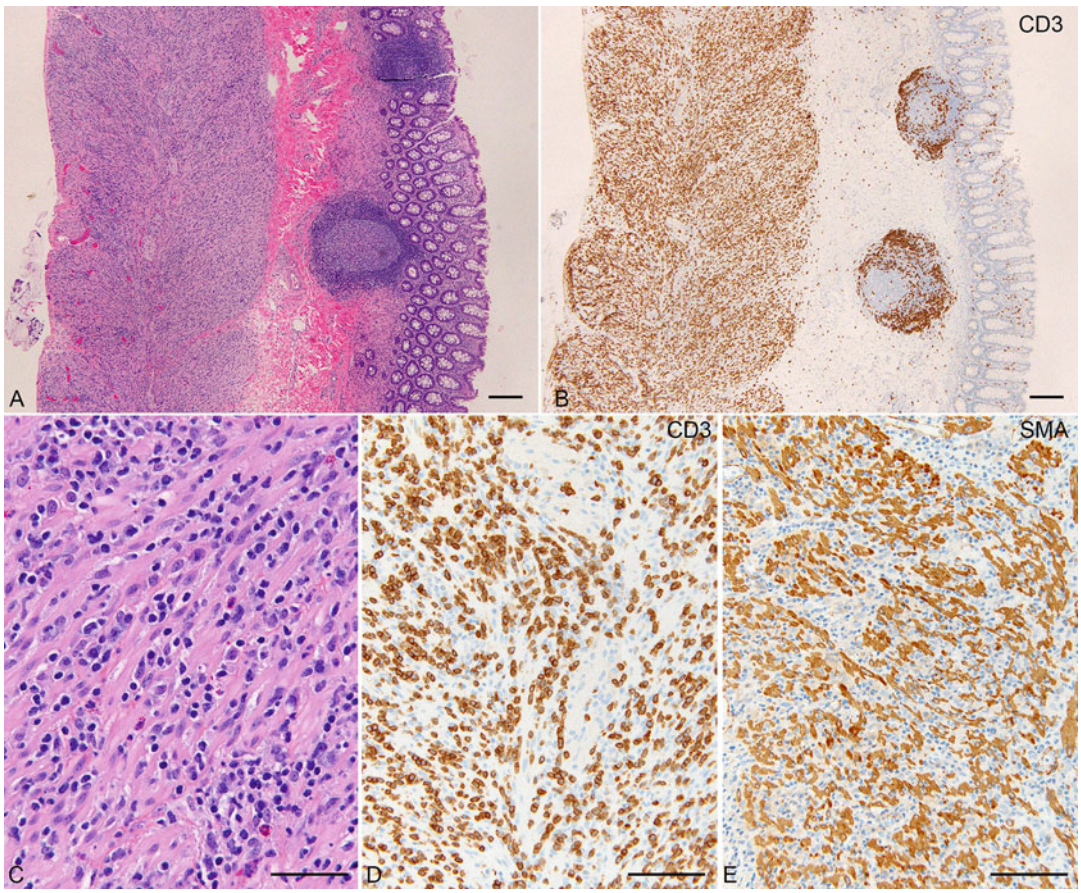

Fig. 17.8 Inflammatory visceral myopathy. (**a**) The muscularis propria (higher magnification in **c**) is diffusely infiltrated by a dense population of mature lymphocytes. (**b**) CD3 immunostaining demonstrates that the lymphocytes are primarily T cells (higher magnification in **d**). (**e**) Smooth muscle actin immunostaining demonstrates smooth muscle fibers, which are widely separated from each other by the inflammatory infiltrate. Scale bars: (**a**–**b**) 200 μm; (**c**–**e**) 100 μm

visceral myopathy include eosinophilic leiomyositis and diffuse lymphoplasmacytic inflammation of the small intestine without myocyte degeneration [83].

Nonspecific Changes

Nonspecific histological changes and artifacts created by tissue handling or processing extend an open invitation for misinterpretation in the pathologist's earnest desire to find clues to the etiology of intestinal pseudo-obstruction. In the muscularis propria, swelling or contraction of smooth muscle cells, possibly related to osmotic changes or delayed fixation, results in a variety of interesting cytological changes. Contraction bands can produce hyper-eosinophilic, actin-rich cytoplasmic globules in individual smooth muscle cells or align nuclei in clusters of adjacent cells to create a pattern of "nuclear stripes" in sections parallel to the long axis of a smooth muscle layer (Fig. 17.9a, b). Pale subsarcolemmal cytoplasmic foci, devoid of actin, can be difficult to distinguish from myodegeneration or increased extracellular matrix, especially without a trichrome stain. Muscular hypertrophy is a common response to chronic increased downstream resistance, and is presaged by increased mitotic activity, as evident in the transition zone of Hirschsprung disease (Fig. 17.9c). Similarly distension can lead to myocyte damage and patchy fibrosis, which is usually more focal and confluent than the patchy or diffuse interstitial fibrosis of primary visceral myopathies. Secondary loss of CD117-immunoreactive interstitial cells of Cajal was discussed above. Similarly, one has to cautiously interpret smooth muscle actin-immunoreactivity, particularly in the distal small intestine, where weak staining of most of the muscularis interna, excluding the innermost layers, is normal [92–94], but has been interpreted as abnormal in some contexts [95–97].

Eosinophilic inflammation of the muscularis propria is a common nonspecific reaction, particularly in distended bowel with bacterial stasis and mucosal injury. In contrast to primary eosinophilic leiomyositis, the muscle does not show degenerative changes and the eosinophilic infiltrates are generally mild and irregularly distributed.

Nonspecific alterations of the myenteric plexus include cytoplasmic hyper-eosinophilia of individual neurons without karyorrhexis, interstitial fibrosis (ganglliosclerosis), lipofuscin accumulation, cytoplasmic vacuolization, and eosinophilic inflammation in the context of Hirschsprung

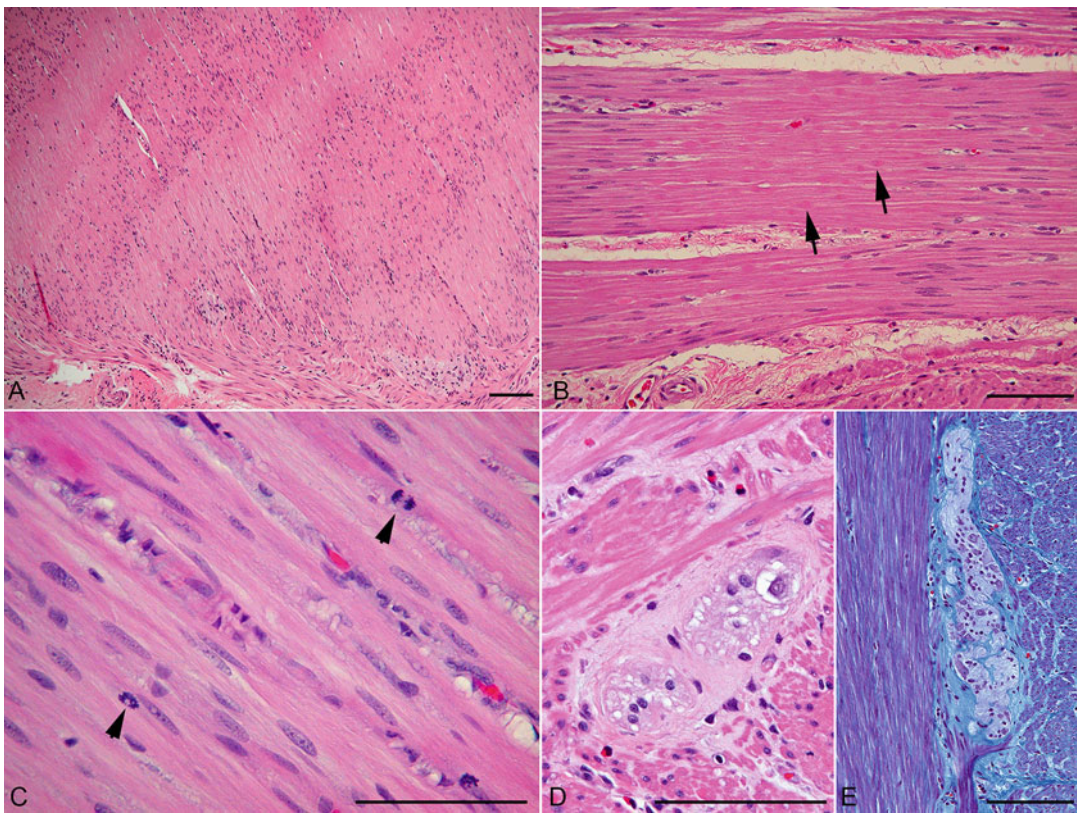

Fig. 17.9 Nonspecific histolopathology. (**a**, **b**) Nuclear palisading is occasionally observed in the muscularis propria, probably as a consequence of peri- or post-resection contraction bands. Alternating stripes of nucleus-rich zones are separated by eosinophilic smooth muscle cell cytoplasms, which may contain globular aggregates of contractile filaments (*arrows* in **b**). (**c**) Mitotic figures in the muscularis propria (*arrowheads*) are often observed proximal to obstructive processes, particularly in neonates. (**d**, **e**) Excessive and hyalinized deposition of collagen (*blue* in **e**) leads to sclerosis of myenteric ganglia, likely as a nonspecific response to distension or inflammation. Scale bars: 100 μm

disease. Ganglionsclerosis (Fig. 17.9d, e) occurs primarily with chronic distension and may represent a response to inflammation or stretch-related trauma. Dense bands of collagen are found around and within ganglia. Although abnormalities in the density of enteric glial cells have been reported in a variety of contexts [98, 99], specific clinical-pathological correlations for myenteric gliosis are not well established.

Intestinal Resections

Resections of bowel from patients with motility disorders are performed in several different contexts. Some of the most common include pull-through procedure (one- or two-stage) for Hirschsprung disease, segmental resection for volvulus, perforation, segmental dilatation, intussusception or atresia, total colectomy for idiopathic chronic slow transit constipation, and intestinal transplantation for generalized enteric myopathies or neuropathies. For most of these specimens, the pathologist's aims are to (a) document any pathological findings, (b) identify or confirm the underlying disease or at least exclude as many conditions as possible from the clinical differential, (c) ascertain whether the disease process extends to the surgical margin(s), and (d) collect and store samples appropriately for ancillary studies or research. The histopathological findings will be similar to those encountered in full-thickness biopsies.

Hirschsprung Disease Pull-Through Specimens

The definitive therapy for Hirschsprung disease is a resection of the neuroanatomically abnormal bowel with anastomosis of normoganglionic bowel a centimeter or so above the anus, usually done transanally by a pull-through procedure. Most of the time, surgery is scheduled after the diagnosis is established by rectal biopsies. Sometimes, the diagnosis is made because of an exploratory laparotomy for spontaneous perforation or intestinal atresia. In rare instances (e.g., healthcare systems in which arrangement for sequential visits is impractical), an intraoperative rectal biopsy is examined by frozen section to establish the diagnosis with an option to move directly to a leveling ostomy or pull through. Given the challenges associated with accurate diagnosis, this practice should be discouraged unless no other option exists. Where the approach is used, rapid AChE histochemistry may be helpful [100].

Whether the pull-through procedure is done in one stage or preceded by a diversion enterostomy, intra-operative frozen section analysis is required to identify ganglion cells and thereby determine an appropriate site ("level") for bowel transection. An appropriate leveling biopsy is at least 3 mm long (>5 mm is ideal) and contains serosa and the full-thickness of muscularis propria with or without submucosa/mucosa. It should be sent immediately to the laboratory on a moist telfa pad.

The biopsy should be oriented in the laboratory such that sections are cut perpendicular to the serosal surface. Most laboratories stain sections with H&E or Diff-Qwik, either of which is fine provided the pathologist has experience with the method. I usually begin with five slides, 2 sections per slide. In a well-oriented, adequate size, nicely sectioned seromuscular biopsy this is almost always sufficient to identify unequivocal myenteric ganglion cells in normoganglionic bowel. Under no circumstances should the pathologist conclude that ganglion cells are present, unless unequivocal ganglion cells are identified. One or more large nerve with extrinsic features in the myenteric plexus is a suggestive, but neither obligatory nor pathognomonic, finding in aganglionic bowel. If necessary, the entire biopsy should be exhausted until an unequivocal ganglion cell is found. If the biopsy is suboptimal (i.e., too little tissue, poorly oriented, crushed, dessicated) the pathologist and surgeon should have a low threshold for re-biopsy at or near the same site. If no ganglion cell is found, additional biopsies should be performed more proximally until ganglion cells are identified by frozen section. Distances between leveling biopsies are at the discretion of the surgeon and may be influenced by considerations of vascular supply and bowel mobilization. Although frozen section of an appendectomy can be used to document appendiceal involvement, aganglionosis of the appendix does not necessarily indicate total colonic aganglionosis, because skip areas (segments of intact colonic innervation) can be present distal to an aganglionic appendix +/− contiguous cecum and distal ileum [101, 102].

It is important that the surgeon resects the entire length of the aganglionic segment and the transition zone of neuroanatomically abnormal bowel found immediately upstream. In truth, anatomic pathology in the transition zone is graded and it is unrealistic to identify subtle differences in neuronal density that may distinguish normal bowel from proximal transition zone. However, moderate-to-severe histopathology is present in the distal part of the transition zone, typically 3–5 cm proximal to the aganglionic segment in short-segment aganglionosis [103]. Specific abnormalities to exclude are partial circumferential aganglionosis (absent ganglion cells along ≥1/8th of the circumference), hypoganglionosis (as described above), and/or hypertrophic submucosal nerves (abundant large submucosal nerves with extrinsic features; two or more submucosal nerves >40 μm in caliber). To improve the likelihood of adequate transition zone resection, I recommend resection of at least 5 cm of ganglionic bowel proximal to the aganglionic segment and evaluation of the full-circumference of the proximal resection margin (so-called margin "donut") by intraoperative frozen section [103]. Orientation of the full-circumference frozen section can be difficult unless one cuts the "donut" into segments and lines them up in the embedding medium similar to books on a shelf.

Once the pull-through resection has been obtained, the minimal work-up must include the following. The length of the specimen should be recorded along with the positions of intraoperative

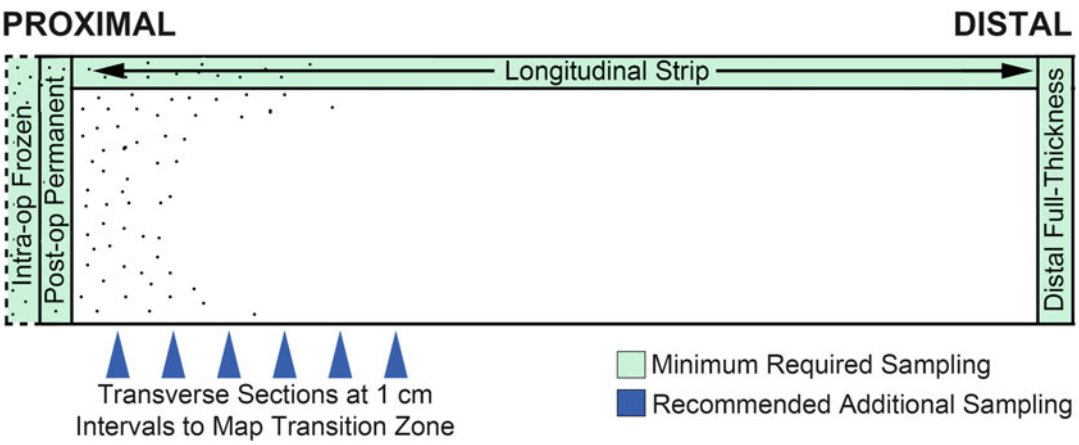

Fig. 17.10 Histological sampling of a Hirschsprung disease pull-through resection specimen. Sections shown in light green should be obtained at a minimum in order to document distal aganglionosis, exclude neuromuscular pathology at the proximal margin, and determine the approximate length of the aganglionic segment. Additional transverse sections at 1 cm intervals through the transition zone (*blue triangles*) may be useful to delineate the length and histopathological features of the transition zone

biopsy sites. I prefer to open and fix the entire specimen flat before sampling for histology, so as to get well-oriented full-thickness sections. After fixation, a transverse section at or near the distal margin should be examined to confirm the diagnosis of aganglionosis. A full-circumference transverse section from the proximal margin should be evaluated to establish a normal density and distribution of ganglion cells, absence of hypertrophic submucosal nerves, and document any other pathology findings likely to be present in the unresected bowel. If an intra-operative frozen section of the proximal margin was performed, permanent sections of the thawed and fixed residual tissue are useful. However, these sections are seldom well oriented and I prefer to also submit an immediately adjacent section from the proximal margin of the fixed specimen. Finally, sections should be submitted to document the length of the aganglionic segment, either by transverse full-circumference sections at close intervals (e.g., 1–2 cm) or a longitudinal strip from the entire length of the specimen (Fig. 17.10). Some pathologists prefer to submit a longitudinal strip as a "jelly roll," whereas others prefer to cut it into segments and use ink to mark the proximal or distal end of each segment. Either approach should resolve the length of the aganglionic segment to within 1–2 cm, recognizing that the interface between ganglionic and aganglionic bowel is irregular, but typically deviates by no more than 3 cm around the bowel circumference [24, 25]. Immunohistochemistry has no meaningful role in the work-up of most HSCR pull-through specimens.

Colectomy for Idiopathic Slow Transit Constipation

For some patients with lengthy histories of idiopathic slow transit constipation, colectomy may be the only therapeutic option [104]. Idiopathic slow transit constipation is usually diagnosed in patients with delayed passage of markers through the large intestine, no megacolon, and ganglion cells in their rectal biopsies. In my experience, pathological evaluation of these colectomy specimens has been a great disappointment. Despite clinical indications of morbid pathophysiology, anatomic changes are minimal and nonspecific. Chronic laxative use and melanosis coli are common. Otherwise, no consistent histopathological phenotype has been established. Hyperganglionosis, hypoganglionosis, and deficient CD117-positive interstitial cells of Cajal have each been reported, but not reproducibly [105, 106]. Some researchers have observed reduced densities of specific subtypes of myenteric neurons (e.g., substance P-immunoreactive), but the pathophysiological relevance of such changes are unclear [107]. My approach is to snap-freeze a few representative full-thickness pieces of colon for possible future use, store small seromuscular samples in electron microscopy fixative, and then obtain representative full-thickness sections at 10–15 cm intervals through the length of the specimen. The aim of histological studies is to exclude recognizable neuromuscular disorders, with immunohistochemistry only if indicated. In most cases, no diagnostic alteration is found.

Conclusions

Our understanding of intestinal neuromuscular pathology continues to advance, in part because of the application of a combination of traditional and new methods larger sets of patients with similar clinical phenotypes. In line with the heterogeneous nature of intestinal motor disorders, the pathology of these conditions is heterogeneous and incompletely defined. The best opportunity for a definitive diagnosis requires good collaboration between clinician and pathologist

with particular attention to proper handling of tissue samples. Many intestinal neuromuscular diseases are rare and may require expertise and/or ancillary studies only available in reference laboratories. Even then, links between histopathological findings and pathophysiology may be speculative or nonspecific. Nonetheless, for an individual patient, sound pathology may lead to a specific diagnosis with clear prognostic and/or therapeutic implications, or at a minimum will exclude many disorders in the clinical differential.

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18 Genetics of Motility Disorders: Gastroesophageal Reflux, Triple A Syndrome, Hirschsprung Disease, and Chronic Intestinal Pseudo-obstruction

Jonathan M. Gisser and Cheryl E. Gariepy

The identification of gene mutations associated with a disease often provides important initial insight into its molecular basis and can hold the key to developing an effective therapeutic strategy. After several decades of identifying single gene mutations causing usually rare GI motility disorders, we are beginning to understand the etiology of complex, multigenic motility disorders. In this chapter we review the current genetic understanding of four motility disorders: gastroesophageal reflux disease (GERD), Triple A syndromic achalasia, Hirschsprung disease, and chronic intestinal pseudo-obstruction. The molecular and developmental consequences of some of these mutations are described in detail in other chapters.

Gastroesophageal Reflux Disease

The lower esophageal sphincter is an anatomic and physiologic barrier that limits the backflow of gastric contents into the esophagus while allowing the passage of food into the stomach. In theory, any developmental process affecting the position and function of the lower esophageal sphincter may result in GERD and be genetically influenced. Moreover, a predisposition to complications of lower esophageal sphincter dysfunction may also be genetically influenced. It is therefore likely that the genetic contribution to the symptoms and complications arising from lower esophageal sphincter dysfunction, commonly referred to as GERD, is multifactorial [1]. Pathophysiologic determinants of GERD that may be genetically modulated have been enumerated [2] and are listed in Table 18.1. Since various definitions of GERD are employed in genetic studies and the disease may be genotypically and phenotypically heterogeneous, no clear genetic determinants have yet emerged [1]. To date, evidence for a genetic predisposition to GERD has been inferred from epidemiologic, twin concordance, and genetic linkage studies, with little attention paid to specific host genetic factors. Evidence supporting genetic risk factors in the development of syndromic GERD and complications from GERD also exists, but is beyond the scope of the present discussion.

The first studies to infer a genetic component to GERD were case reports describing familial clusters of radiologically confirmed hiatal hernia (reviewed in [3]). In the largest and most detailed of these studies, Carre and colleagues described a kindred of 38 family members across five generations, all of whom were interviewed and subjected to a barium meal. Among this pedigree were 20 individuals with both symptoms of gastroesophageal reflux, and radiologic evidence of hiatal hernia. An autosomal dominant mode of inheritance was suggested [4].

Although familial clusters of hiatal hernia are established, most cases of hiatal hernia are sporadic and most pediatric GERD is not associated with hiatal hernia. Therefore hiatal hernia probably accounts for a small minority of cases of hereditary GERD. Other studies support a familial predisposition to GERD even in the absence of a hiatal hernia. In case control studies, GERD symptoms in relatives of patients with Barrett's metaplasia, and esophageal adenocarcinoma were more prevalent than in spouse controls. A similar increased prevalence among relatives of patients with uncomplicated esophagitis was not observed in this study, suggesting that only severe GERD is heritable [5]. However, another investigation of patients with abnormal pH studies revealed that relatives of patients with increased esophageal acid exposure were more likely to experience frequent reflux symptoms, even in the absence of GERD complications [6].

Familial clustering of GERD can also arise from shared environmental risk factors rather than genetic factors. In twin studies, conditions that bear a large genetic predisposition are more likely

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Table 18.1 Pathophysiologic determinants of gastroesophageal reflux disease that could be genetically modulated

Refluxate toxicity
Gastric acid secretion
Duodenogastric reflux
Intrinsic gastric volume and pressure
Gastric compliance
Gastric emptying
Gastric acid volume secretion
Extrinsic pressure on gastric contents
Weight (obesity)
Somatic motor tone (spasticity)
Somatic and crural episodic contractions (cough, wheeze, others)
Gastroesophageal barrier
Lower esophageal sphincter tone
Gastric fundic sensory thresholds (for transient lower esophageal sphincter relaxations)
Crural diaphragm location (relative to sphincter location) and function
Esophageal defenses
Salivary secretion
Peristaltic motor function
Esophageal cytoprotection

Adapted from Orenstein SR, Shalaby TM, Barmada MM, Whitcomb DC. J Pediatr Gastroenterol Nutr. 2002;34(5):506–10. Lippincott Williams & Wilkins, Inc., Philadelphia, publishers

concordant in monozygotic twins than dizygotic twins. Two large-scale studies have investigated the concordance of GERD in mono- and dizygotic twins. In one of these studies, twins belonging to the national Swedish Twin Registry were queried for GERD using a questionnaire. In almost 3100 twin pairs with GERD, aged 55 years or greater, the concordance was significantly higher among monozygotic twins compared to dizygotic twins, suggesting that heritability accounts for approximately one-third of the susceptibility to GERD [7]. A similar study from a twin registry in the United Kingdom corroborated the Swedish study, finding concordance rates of 42% for monozygotic twins versus 26% for dizygotic twins, and concluding that 43% of the predilection to GERD is genetically influenced [8].

In an attempt to detect specific genetic loci associated with GERD, Hu and colleagues performed a genetic linkage analysis of five families in which multiple family members were afflicted with severe pediatric GERD. They found a 9-centiMorgan locus on the long arm of chromosome 13 (13q14; termed GERD1) that segregated with the severe pediatric GERD phenotype in their cohort [9]. A candidate gene in this region is the 5-hydroxytryptamine receptor 2A. However, no coding sequence mutations were identified [9, 10]. The authors proposed that mutations in regulatory or other noncoding regions, null alleles, segmental deletions and duplications, and epigenetic effects in the 13q14 region could still account for the pediatric GERD phenotype in these families [10]. In support of this, a case report describes a dysmorphic infant with severe GERD who possesses a 12.8 megabase deletion spanning the GERD1 locus, implicating GERD1 haploinsufficiency in the patient's symptoms [11]. However, independent linkage analyses in different cohorts failed to confirm the association of the 13q14 locus with GERD [2, 12] underscoring the genetic heterogeneity of GERD.

The subjective sensation of GER has been attributed to the exposure of esophageal mucosa to the acidic gastric refluxate causing a mucosal inflammatory response which, in turn, activates afferent sensory nerve pathways. As such, variations in genes that participate in inflammation, wound healing, and sensory neuromodulation could theoretically contribute to the experience of gastroesophageal reflux. With this in mind, three recent studies have focused on genes in these pathways. A study by Chourasia et al. evaluated the relationship of polymorphisms in genes encoding the Interleukin 1B (*IL-1B*) and the interleukin one receptor antagonist (*IL-1RN*) to GERD in patients referred to a tertiary center [13]. A single nucleotide polymorphism in the promoter region of the *IL-1B* gene predisposes to increased concentrations of IL-1beta, a potent pro-inflammatory cytokine. In contrast, a polymorphism consisting of two intronic tandem repeats (as opposed to 3–5 repeats) within the *IL-1RN* gene tends to decrease IL-1beta levels and has an anti-inflammatory effect. Hypothesizing that increased gastric inflammation destroys proton-excreting parietal cells, thus lowering esophageal acid exposure, investigators characterized the IL-1 genotypes of 144 patients with confirmed GERD and 368 healthy controls. They found that subjects with genotypes and haplotypes combining to decrease IL-1beta levels had predictably lower gastric mucosal IL-1beta expression, and generally had a higher risk of GERD. These genotypes and haplotypes were also more prevalent in the GERD population [13].

In another genome-wide association study, Asling and colleagues collected 36 GERD-affected families and mapped familial GERD to a 35 megabase pair region on chromosome 2q24-q33, confirming this association in a separate cohort. Biopsies from those subjects with abnormal endoscopic or pHmetric findings, or those who had undergone fundoplication, were then subjected to gene expression analysis and the COL3A1 gene (collagen type III alpha I), residing within this locus, was found to be differentially expressed in subjects with GERD compared to controls. As collagen type III contributes to tissue strength, flexibility, and wound response, the authors proposed a mechanism whereby altered collagen type III expression in the esophagus results in a predisposition to esophageal damage in patients with gastroesophageal reflux. Although they immunohistochemically demonstrated increased expression of the collagen III protein in esophageal tissue biopsies, they did not investigate whether this was a cause or a consequence of gastroesophageal reflux. Also, sequencing of the COL3A1 gene in 48 subjects did not identify any causative mutations. The authors propose that disease-causing mutations reside in regulatory regions [12].

G-proteins are second messengers involved in the neurotransmission of gastroesophageal sensation. The C825T substitution polymorphism within the gene encoding the G-protein β3 subunit results in enhanced G-protein activation and signal transduction [14], and is associated with functional dyspepsia [15]. On this basis, De Vries and coworkers explored the relationship of the C825T allele with GERD in 363 subjects with either pathologic esophageal acid exposure or a positive symptoms association score for heartburn or regurgitation. Compared to healthy controls, individuals with GERD were more likely to be heterozygous for the C825T. The likelihood of being heterozygous for C825T was highest (adjusted odds ratio 1.5; 95 % CI 1.06–2.13) among patients with a positive symptom association score, but no correlation was observed among those with pathologic acid exposure. This suggests that enhanced perception of physiologic acid exposure, and not pathologic acid exposure, underlies the association of C825T heterozygosity and GERD [16].

More recently, larger databases of better characterized subjects have enabled more statistically powerful genome-wide association studies quantifying the genetic contributions to GERD. Ek et al. analyzed a Swedish cohort of 994 subjects and over 600,000 Single Nucleotide Polymorphisms (SNPs), and did not identify a genetic contribution to the risk of GERD, probably because this study was still limited by an inadequate sample size [17]. More recently, however, interrogation of the Barrett's and Esophageal Adenocarcinoma Consortium (BEACON) and the 23 and ME discovery cohorts, which contain detailed information on heartburn and regurgitation symptoms from almost 10,000 GERD cases, demonstrated for the first time that GERD has a polygenic background, but that no individual specific SNPs conferred GERD susceptibility [18]. However, using a specific set of SNPs, they were able to predict the risk of GERD in an independent target cohort and there was an estimated SNP heritability of 7 % (95 % CI 3–11 %). It should be noted that these were adult studies and the genetic underpinnings of GERD in children may differ.

Each of the above studies propose different heritable host factors in the pathophysiology of GERD, increasing the likelihood that still other host factors exist. Furthermore, replication and validation of existing studies is required, highlighting the great need for further investigation in this area.

Triple A Syndrome

Triple A syndrome (AAAS) is a condition characterized by *a*lacrima, adrenocorticotrophic hormone-resistant *a*drenal insufficiency, and *a*chalasia [19]. Although its name connotes a triad, the syndrome is phenotypically heterogeneous: fewer than three features may be present and additional features not originally identified in the initial report by Allgrove, including progressive autonomic, central, and peripheral nervous system deficits, are associated with the syndrome [20]. The etiology of achalasia in AAAS appears to be distinct from other forms of achalasia [21]; in contrast to idiopathic achalasia, which does not segregate in families, AAAS is a genetic disorder. Although it is a rare condition and epidemiologic data are scant, symptoms of swallowing difficulty and achalasia in AAAS usually manifests by the end of the first decade of life and can begin in infancy [22, 23]—in contrast to idiopathic achalasia, where very small minority of patients manifest symptoms before 10 years of age [24]. However, there is also a late-onset form of AAAS [25]. The diagnosis of achalasia in AAAS relies on the same manometric, radiographic, and endoscopic criteria as for idiopathic achalasia, and the treatment is similar. However, AAAS is thought to follow a more severe course [26].

Frameshift, point, or missense mutations in the gene *AAAS*, located at 12q13, account for the majority of cases of AAAS [20, 27, 28]. Consanguinity is often present in kindreds of AAAS and the condition mostly segregates in an autosomal recessive pattern, but compound heterozygous mutations in *AAAS* have resulted in AAAS, sometimes with pleiotropic effects. In total, greater than 70 homozygous or compound heterozygous mutations have been identified [29]. The penetrance of AAAS with bi-allelic mutations in *AAAS* approaches 100 %, though expressivity is variable, possibly due to abovementioned allelic variation or the existence of as yet unidentified modifier genes. Conversely, others have reported a very tight genotype–phenotype correlation [30].

AAAS encodes the ALADIN protein (an acronym for alacrima, achalasia, adrenal insufficiency and neurological disorder) [31, 32]. ALADIN is part of the nuclear pore complex, a large, multiprotein complex spanning the nuclear envelope and forming a selective channel between the cytoplasm and the nucleus [33, 34]. ALADIN is the first nuclear pore protein linked to a human heritable disease. In most cases of AAAS, ALADIN is truncated, resulting in its exclusion from nuclear pore complex and in ectopic cytoplasmic accumulation. This may be due to an inability of the mutant ALADIN protein to anchor to proteins required for nuclear pore complex assembly [35] or to the deletion of a critical nuclear localization signals in the *AAAS* transcript [36]. Although the nucleus and the nuclear pore complex remain morphologically and structurally intact without ALADIN, the nuclear import of selected proteins is interrupted. Proteins involved in DNA repair and the attenuation of oxidative stress fail to localize to the nucleus when ALADIN is absent from the nuclear pore complex [37, 38]. On this basis, it is proposed that defective ALADIN renders cells susceptible to oxidative DNA damage and cell death in a tissue-specific manner [37]. In support of this, fibroblast cultures derived from patients

with AAAS possess a higher basal level of reactive oxygen species, a heightened response to oxidative stress and a predilection for premature stress-induced senescence [39]. Similar findings were observed in an *AAAS* knockdown cell line model [40].

In addition to its role in redox homeostasis, ALADIN may also be required for proper mitotic spindle assembly, as artificially depleting human cells of ALADIN in vitro slows spindle assembly and chromosome alignment, by disrupting the recruitment of other spindle proteins (Aurora A) [41]. Indeed, the observation that mitotic errors are common in triple A patient fibroblasts supports the possibility that mitotic defects also play a role in AAAS.

Given the variety and abundance of macromolecules that depend on a competent nuclear pore complex and a functional mitotic spindle, it is probable that additional genes and proteins will one day be identified that will further elucidate how the ALADIN defect translates into the observed phenotypes of AAAS.

Hirschsprung Disease

Hirschsprung disease (HSCR) is the developmental abnormality resulting from the failure of vagal neural crest cells to complete colonization of the developing intestine between the 5th and 12th week of gestation [42, 43]. A minority of HSCR (30%) is syndromic (associated with other congenital anomalies) with several monogenic syndromes recognized and chromosomal abnormalities found in 12% of cases. The overt abnormality is the absence of intramural ganglion cells in the myenteric and submucosal plexuses of the rectum and a variable length of contiguous bowel. HSCR is classified by length of aganglionosis into short-segment (70% of cases), long-segment (20% of cases) with aganglionosis rostral to the splenic flexure, and with total colonic (10% of cases) aganglionosis.

HSCR is a sex-modified, multifactorial genetic disease [44]. Males are affected more frequently than females with the gender bias being higher for short-segment (4.2–4.4) than for long-segment disease (1.2–1.9) [44]. HSCR is associated with other congenital anomalies in 30% of cases including recognized syndromes (18%) and chromosome abnormalities (12%) [45]. Associated anomalies include pigmentary, sensorineural, craniofacial, urogenital and gastrointestinal (atresia/stenosis of the colon, rectum, anal canal), cleft lip/palate, polydactyly, and cardiac defects. HSCR is a mandatory feature of 11 syndromes, including Shah-Waardenburg, Goldberg–Shprintzen, Mowat–Wilson, and Congenital Central Hypoventilation (CCHS) syndromes, and a non-obligate finding in 30 others, such as Bardet–Biedl, Kaufman–McKusick, and Smith–Lemli–Opitz syndromes. Trisomy 21 (2–10% of cases) and deletion/duplication of chromosome 17q21-23 are common, as are large deletions of *RET*, *EDNRB*, and *ZFHX1B* [45]. The complex genetics of HSCR is reflected in its varied phenotype, recurrence risk, and penetrance in families, features that modulate its presentation and clinical outcome.

Genetic studies have identified rare high-penetrance mutations in 13 genes (*RET*, *GDNF*, *NRTN*, *SOX10*, *EDNRB*, *EDN3*, *ECE1*, *ZFHX1B*, *PHOX2B*, *KBP*, *TCF4*, *L1CAM*, and *IKBKAP*) predominant in syndromic HSCR [46]. Recent exome sequencing studies have identified several new genes [47, 48]. Approximately 30% of patients have one of these rare mutations [49].

In contrast, three common noncoding and low-penetrance variants at *RET* (rs2435357, rs2506030, and rs7069590) [50, 51] and at least one each at *NRG1* (rs4541858) [52] and *SEMA3C/D* (rs11766001) [53] contribute to pathogenesis and length of aganglionosis in isolated HSCR. All three noncoding variants of *RET* increase disease risk through significant reduction of binding of the transcription factors SOX10, RARB, and GATA2 to *RET* enhancers, leading to reduced RET expression in the developing gut. Kapoor et al. analyzed these variants in 997 samples from 376 HSCR families of European ancestry and reported that individuals with one or fewer risk alleles (~50% of the population) have an estimated risk of ~1/20,000 live births and those with two risk alleles (27.3% of the population) have a background risk of HSCR at ~15/100,000 live births. However, individuals with three or more risk alleles (23.3% of the population) have an increased HSCR risk varying from 1.6- to 9.5-fold. Those with five or six risk alleles have an estimated risk of ~1/800 live births. Thus there is a 32-fold range in risk based on these alleles, with an odds ratio varying from 0.3 to 9.5 between those with 0 versus 5 or 6 alleles. The variations are even more marked when individuals are classified by gender [49]. Overall, HSCR can be caused by the segregation of multiple common and rare variants in at least 23 genes and 15 chromosomal loci but a *RET* loss-of-function allele appears to be necessary for disease expression [49].

The genes implicated in HSCR affect the migration, proliferation, survival, and/or differentiation of all enteric neural precursors, as well as the many other cell types in other organs. Consequently, the multifactorial nature of HSCR gene defects disrupts other aspects of development. The range of associated defects is wide, including obvious congenital malformation and increased risk of neoplasia in adults.

RET is a proto-oncogene that is disease causing in Multiple Endocrine Neoplasia syndrome 2 (MEN2), congenital abnormalities of the kidney and urinary tract, and HSCR [54]. The majority of *RET* coding sequence mutations that cause HSCR are loss-of-function mutations that either result in early truncation or reduced function of the protein. However, gain-of-function mutations have also been identified in HSCR. These gain-of-function mutations overlap the mutations causing MEN2A and medullary thyroid carcinoma (MTC). MEN2A

mutations occur in a cluster of cysteines on exon 10 or exon 11. HSCR and MEN2A occur together in some patients and families, requiring a more complex explanation for the signaling consequences of these mutations [55]. Exon 10 mutations account for all cases of HSCR associated with MEN2A, with the C620 mutation being the most common [56]. The mechanism of the dual loss-of-function and gain-of-function actions of these mutations is not fully understood. A provocative long-term follow-up study from Finnish Cancer Registry of an unselected group of 156 adults with HSCR screened for thyroid malignancy genetically and clinically found MTC or MTC-producing RET mutations in 5 % of the group (including both exon 10 and exon 13 RET mutations). They emphasized that clinical thyroid assessment did not improve the accuracy of the genetic screening and that length of aganglionosis did not correlate with the risk for thyroid malignancy. These researchers advocate for genetic screening of all individuals with HSCR [57].

Syndromic HSCR

A wide range of isolated anomalies are reported with HSCR. Cardiac defects (most commonly atrial- or ventricular-septal defects) and renal anomalies are found in ~5 % of HSCR patients and should be looked for systematically. For HSCR associated with other congenital anomalies, the prognosis is largely dependent on the severity of the other anomalies. Numerous syndromes are associated with HSCR and the recognition of these syndromes is important for disease prognosis and accurate genetic counseling. Careful evaluation by a clinician familiar with the varied associated syndromes is extremely valuable to the patients and their families. Below we discuss syndromes most commonly associated with HSCR.

HSCR occurs in syndromes with defects in other neural crest-derived tissues, termed neurocristopathies. The neural crest is a transient, multipotent, migratory cell population in the embryo that give rise to diverse tissues of the body, including melanocytes, craniofacial cartilage and bone, cells in the thymus, the cardiac outflow tract, the adrenal medulla, the autonomic nervous system, and the ENS. Congenital central hypoventilation syndrome (CCHS) is an autosomal dominant neurocristopathy characterized by an abnormal ventilatory response to hypoxia and hypercapnia due to abnormal autonomic respiratory control. The syndrome can be associated with broader dysfunction of the autonomic nervous system and with neural crest-derived tumors (5–10 % of CCHS patients develop neuroblastoma, ganglioblastoma, or ganglioneuroma). CCHS is caused by mutation in *PHOX2B* with a de novo heterozygous in-frame duplication leading to polyalanine expansion being the most common mutation identified. However, approximately 10 % of the parents of CCHS patients will be mosaic for the mutation and may develop late onset central hypoventilation. There is also a clear genotype–phenotype correlation with the risk for tumor development: individuals carrying the most common polyalanine expansion mutation can be reassured, while those carrying a frameshift mutation are at high risk and should be considered for regular screening [58, 59]. Overall, 20 % of individuals with CCHS have HSCR with L-HSCR or TCA being most common with a near equal male-to-female ratio [60]. However, the T allele of RET affects the penetrance of HSCR with the incidence of HSCR climbing to 60 % in CCHS patients homozygous for the T allele [61].

The combination of Waardenburg syndrome and HSCR is termed Waardenburg syndrome type 4 (WS4) or the Shah-Waardenburg syndrome. It is called by homozygous mutations of the endothelin-B signaling pathway (*EDNRB* or *EDN3*) or heterozygous *SOX10* mutation. Patients with *SOX10* mutations are additionally at risk for other neurologic abnormalities including seizures, ataxia, and demyelinating neuropathies. HSCR is associated with severe congenital deafness in the absence of pigment abnormalities [62].

HSCR also occurs in syndromes that are not neurocristopathies. Trisomy 21 increases the risk of HSCR by 40-fold (0.8 % of individuals with trisomy 21 have HSCR) and is by far the most frequent chromosomal abnormality identified in HSCR patients, involving 2–10 % of HSCR. HSCR in patients with trisomy 21 shows a more pronounced male predominance and is primarily S-HSCR [63]. Interestingly, the T allele in *RET* intron 1 enhancer discussed above appears to play a role in the expression of HSCR in trisomy 21 as well as sporadic, non-syndromic HSCR. While the incidence of the T allele is higher in individuals with trisomy 21 HSCR than in individuals with trisomy 21 alone, it is less than that observed in individuals with HSCR alone. This suggests interaction between RET and chromosome 21 genes, perhaps through a reduced HSCR threshold conferred by the extra chromosome 21 [64].

Mowat–Wilson syndrome includes microcephaly, epilepsy, facial dysmorphism, and severe mental retardation. Sixty percent of affected individuals have HSCR. The syndrome is caused by heterozygous de novo inactivating mutations of *ZEB2* [65]. Goldberg–Shprintzen syndrome includes microcephaly, polymicrogyria, facial dysmorphism, cleft palate, iris coloboma, and moderate mental retardation. It is caused by mutation in the gene encoding the kif-1 binding protein (known as *KBP* or *KIAA1279*) [67]. Animal models suggest that this protein is required for axonal outgrowth in the central and peripheral nervous system and for axonal maintenance [67]. Drevillon et al. demonstrated that KBP protein interacts with microtubules and actin filaments, suggest that the multiple developmental anomalies seen in Goldberg–Shprintzen syndrome might originate from disruption of cytoskeletal homeostasis [68].

Bardet–Biedl syndrome (BBS) includes progressive pigmentary retinopathy, hypogonadism, renal abnormalities,

mild mental retardation, obesity, and postaxial polydactyly of the hands and feet. HSCR is reported in several cases. It is caused by at least 14 different genes all of which are involved in the function of primary cilia [69]. As with trisomy 21, *PHOX2B* and *EDNRB* mutations, the presence of the T allele of *RET* associated with expression of the aganglionosis phenotype despite independent biochemical signaling pathways [61]. McKusick–Kaufman syndrome is a rare condition allelic to BBS that includes hydrometrocolpos, postaxial polydactyly, and congenital heart defects. HSCR is reported in 10 % of cases [70].

Smith–Lemli–Opitz syndrome is characterized by growth retardation, microcephaly, severe mental retardation, dysmorphic facies, hypospadias, and syndactyly of the toes. A high percentage of patients also have HSCR. The syndrome is due to mutation in a gene involved in cholesterol metabolism, 7-dehydro-cholesterol reductase [71]. HSCR occurs with limb anomalies in several other rare syndromes. See Table 18.2 for more on the genetics of isolated and syndromic forms of HSCR.

Chronic Intestinal Pseudo-obstruction

Chronic intestinal pseudo-obstruction (CIPO) is a heterogeneous group of rare primary and secondary disorders in which ganglion cells are present throughout the GI tract in a patient with severe failure of intestinal propulsive motility. The anatomic correlates of CIPO are most often absent, subtle, subjective, or nonspecific. Most cases are sporadic and non-syndromic, but familial and syndromic forms exist. CIPO is generally divided into three groups: neuropathic, mesenchymopathic, and myopathic, depending upon whether predominant abnormalities are found in the enteric nervous system, Interstitial Cells of Cajal (ICC), or intestinal smooth muscle, respectively. While a genetic basis is suspected in a large percentage of CIPO, it is established in only a small minority of cases.

Neuropathic

Intestinal Neuronal Dysplasia type B (IND B) is characterized by hyperplasia of the submucosal and mucosal portions of the enteric nervous systems, presents with chronic constipation in

Table 18.2 Genetics of isolated and syndromic forms of Hirschsprung's disease

Gene	Mutation	Phenotype
A. Isolated Hirschsprung		
RET	Heterozygous loss-of-function of tyrosine kinase receptor (many identified)	Long-segment or total-colonic disease more common
EDNRB	Heterozygous loss-of-function of G protein-coupled receptor	Generally produces short-segment disease
B. Syndromic Hirschsprung		
RET	Heterozygous mutations of cysteines producing constitutive dimerization and activation of the receptor	MEN2A: medullary thyroid carcinoma, pheochromocytoma, parathyroid hyperplasia
Phox2B	Heterozygous loss-of-function mutation of transcription factor, polyalanine expansion most common	Congenital central hypoventilation syndrome: abnormal autonomic respiratory control, frame-shift mutations increase risk of neuroblastoma
EDNRB	Homozygous loss-of-function mutation of G protein-coupled receptor	Waardenburg syndrome type 4: pigment abnormalities, deafness. Sox10 mutations also associated with ataxia, neuropathies, and seizures
ZEB2	Heterozygous loss-of-function mutation of transcription factor	Mowat–Wilson syndrome: microcephaly, epilepsy, dysmorphic face, cognitive impairment
KIAA1279	Homozygous loss-of-function in protein involved in microtubule organization	Goldberg–Shprintzen syndrome: microcephaly, polymicrogyria, dysmorphic face, cleft palate, iris coloboma, mild cognitive impairment
BBS genes	Homozygous loss-of-function in proteins involved in primary cilia	Bardet–Biedl syndrome: obesity, renal abnormalities, polydactyly, retinitis pigmentosa, hypogonadism, cognitive impairment
DHCR7	Homozygous loss-of-function of enzyme in cholesterol production pathway	Smith–Lemli–Opitz syndrome: microcephaly, dysmorphic face, hypotonia, syndactyly, polydactyly, ambiguous genitalia, poor growth
C. Modifying genes		
RET	T allele: single nucleotide substitution in an enhancer sequence	This common allelic variant increases the penetrance of Hirschsprung disease in those with other genetic susceptibilities, like trisomy 21, mutations in EDNRB, Phox2B, and BBS genes

the first 6 months of life, and is reported in the proximal gut of some individuals with HSCR [72, 73]. Children with isolated IND B often improve in GI function over time with conservative treatment and do not progress to CIPO [74]. While the diagnosis of IND B remains controversial, several animal models and its association with HSCR suggest a genetic cause. IND-like hyperplasia of submucosal ganglia occurs in the proximal gut of EDN3-deficient mice [75] and in the small intestine and colon of apparently healthy *EDNRB* heterozygous rats [76], both models of HSCR. Attempts to identify mutations in EDNRB in IND B patients have been unsuccessful [77] but Swaminathan et al. recently described IND B-like submucosal ganglion hyperplasia in the proximal margins of HSCR resections [78].

IND A is a rare, fatal syndrome of aplasia or hypoplasia of the enteric sympathetic nerves which presents in the immediate neonatal period with a tonically contracted intestine [79]. The genetics of the disorder are unknown.

Neurofibromatosis 1 (NF1) is a neurocristopathy associated with disordered intestinal motility related to neuroglial proliferation and often tumor formation in the submucosal and myenteric plexus. It is also associated with HSCR. Fifty percent of cases result from de novo mutations and 50 % are inherited in an autosomal dominant fashion with highly variable penetrance and phenotypic expression. The NF1 gene encodes neurofibromin which is an upstream regulator of the RAS/RAF/MAPkinase and RAS/RAL intracellular signaling pathways [80]. A *GDNF* mutation modifies the enteric phenotype of NF1. Individuals carrying both the neurofibromin and *GDNF* mutation develop NF1 with congenital intestinal dysmotility associated with submucosal plexus hyperplasia [81].

MEN2B is a rare autosomal dominant syndrome characterized by medullary thyroid carcinoma, pheochromocytoma, marfanoid appearance, and ganglioneuromas. The syndrome is most often caused by activating mutation of codon 918 of *RET*. Because 50 % of mutations are de novo, a family history is frequently absent. Constipation, often severe, related to intestinal ganglioneuromatosis is present in 40 % of patients and may be present at birth [82, 83]. Recognition of this potential cause of severe constipation is clinically important because the intestinal symptoms usually precede endocrine neoplasia. Individuals with MEN2B *RET* mutations develop early onset MTC with metastatic disease reported in infants. Total thyroidectomy during the first month of life is recommended [84].

In addition to being associated with pigment abnormalities and HSCR (WS4), *SOX10* mutations are associated with additional nervous system symptoms, including nystagmus, hypotonia, cerebellar ataxia, and peripheral demyelinating neuropathy [85]. Occasionally the enteric phenotype in individuals with *SOX10* mutations is not HSCR but CIPO with normal appearing ganglia [86].

Two cases of an X-linked form of neuropathic CIPO have been reported. One was associated with mutations in filamin A (FLNA) and one to mutations in the L1 cell adhesion molecule [87, 88]. However, in-depth histopathologic studies suggest that CIPO caused by FLNA mutations may be myopathic and not neuropathic [89].

Mutations in RAD21 occur in a family with autosomal recessive CIPO associated with Barrett esophagus and cardiac abnormalities (Mungan syndrome). Bonora et al. described an essential role for RAD21 in ENS development using a zebrafish model [90].

Mesenchymopathic

The ICC are derived from mesenchymal precursor cells and are located adjacent to the myenteric plexus (ICC-MY), along the submucosal boarder of the circular muscle (ICC-SM), within the circular muscle layer in the deep muscular plexus (ICC-DMP), and within muscle bundles of the tunica muscularis (ICC-IM). Various mutations in the gene encoding the receptor tyrosine kinase KIT and its ligand, stem cell factor, produce reductions in some classes of ICC. A reduction in ICC-MY results in mice without intestinal pacemaker activity, a reduction in ICC-IM results in marked reduction in cholinergic excitatory and nitrergic inhibitory input to intestinal smooth muscle. Animal models with genetic reduction in ICC exhibit abnormal intestinal motility patterns without signs of intestinal obstruction, while animals with antibody-mediated ICC reduction in the neonatal period exhibit dysmotility with distension [91, 92]. This likely relates to the severity and subtype of ICC reduction. The absence of ICCs, their abnormal distribution or morphology is suggested to cause CIPO based on several case reports [93].

Myopathic

Myopathic CIPO usually includes a variety of extraintestinal manifestations and myopathies. The megacystis-microcolon-intestinal-hypoperistalsis syndrome, MMIHS, is characterized clinically by intestinal and urinary dysfunction and histologically by a reduction in the expression of contractile and cytoskeletal proteins in the intestinal and bladder smooth muscle. Variants of the ACTG2 gene, encoding gamma 2 enteric actin, a protein crucial for correct enteric muscle contraction, have been found in CIPO patients affected with congenital or late-onset visceral myopathy. Matera et al. detected heterozygous missense variants affecting highly conserved regions in ACTG2 in 9 of 23 patients with MMIHS or CIPO. Interestingly, a large number of these patients were initially diagnosed with IND B and suspected to have intestinal neuropathy. This highlights the importance for CIPO classification and the need for detailed correlations between histopathological findings, clinical phenotypes, and genetic defects in CIPO [94, 95].

A significant fraction of pediatric and adult CIPO patients have mitochondrial defects. These patients almost invariably have or will develop extra-intestinal neurologic or muscle

symptoms [96]. A loss-of-function mutation in the thymidine phosphorylase gene (*TYMP*) produces the mitochondrial neuro-gastro-intestinal encephalomyopathy (MNGIE) syndrome, a rare autosomal recessive condition beginning in the second decade of life and characterized by CIPO, ptosis, progressive external ophthalmoplegia, peripheral neuropathy, and leukoencephalopathy. Related disorders include MNGIE without leukoencephalopathy that can be caused by mutation in the mitochondrial DNA polymerase gamma gene (*POLG*) leading to mitochondrial depletion, and MELAS (mitochondrial myopathy, epilepsy, lactic acidosis, and stroke-like episodes) caused by mutation in a mitochondrial transfer RNA [97–99].

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Allergy and Neurogastroenterology

19

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Allergic conditions such as allergic rhinitis, eczema, and food allergy appear to be more prevalent than ever before suggesting that we may be in the midst of a global allergy epidemic. Allergic phenomena by definition are immune mediated disorders and therefore it is perhaps not surprising to see them in the gastrointestinal (GI) tract given it contains prolific amounts of immune cells and tissue. Although there has been much debate on the issue, there appears to be a true rise in prevalence of GI allergic manifestations, including motility disorders, perhaps mirroring the rise of other immune-mediated GI diseases such as Crohn disease. For the purposes of this chapter the terms "GI allergy" and "food allergy" will be used interchangeably.

Food allergy is common, affecting 6–8 % of children. The prevalence is highest in infants and toddlers, with 2.5 % of infants suffering from milk allergy and up to 10 % of 1-year-olds suffering from food allergies, including cow's milk, egg, nuts, soya, wheat, and fish/shellfish [1–3].

Cow's milk protein (CMPA) allergy appears to be the most common food allergy in infants with an incidence of CMPA in early childhood of approximately 2–3 % in developed countries and suggestive symptoms reported in 5–15 % [4]. CMPA has been identified as a global problem [5].

Food allergy is increasingly implicated in common gastrointestinal motility and functional disorders such as gastroesophageal reflux, recurrent or functional abdominal pain, diarrhea, and constipation. The definitive diagnosis of allergy in these conditions, however, is difficult and their management by dietary manipulation a matter of great debate. This chapter aims to review the putative mechanisms for allergy in motility disorders including neuro-immune dysregulation and the evidence for its role. It should be noted that chapters on individual conditions in this book make reference to allergy and its related management, which this chapter will not seek to do.

Gastrointestinal Food Allergy

Definition and Types

GI allergy generally represents an adverse immune response towards food proteins, hence the term "food allergy," accepting that other environmental allergens may also play a role. It is broadly divided into IgE-mediated (immediate type, type I hypersensitivity) or non-IgE mediated (delayed, cell-mediated type IV or IgG/IgM immune complex-mediated type III hypersensitivity). This distinction is based on clinical features, the presence of food-specific IgE measurements, the results of food challenge, and other auxiliary tests such as blood, skin prick, and patch tests as well as endoscopic and pathologic evaluation. In practice, the distinction is less clear with overlapping features of both type I and IV/III allergy [6, 7].

Non-IgE mediated, delayed type, pathways appear to predominate in GI allergy complicating the process of diagnosis by shifting reliance away from commonly applied IgE tests towards more crude monitoring of symptoms following exclusion from, and exposure to, food antigens.

Aetiopathogenesis, Manifestations, and Diagnosis

The immunopathogenesis of food allergy and manifestations of various food-induced allergic disorders appear to involve a complex interplay between the environment and genetics. Enmeshed within this are implications from dysregulation of immune function including loss of oral tolerance, reduced

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exposure to microbes, dysbiosis of the intestinal microbiome, prolonged avoidance of allergen exposure, and processes that increase sensitization to (food) antigens including food preparation and processing. There may also be a relationship with male sex in childhood, more affluent lifestyle, and race/ethnicity [8, 9].

Type I hypersensitivity reactions occur when patients develop IgE antibodies to antigenic epitopes present on specific food proteins or peptides. Their binding to IgE receptors on the surfaces of mast cells and basophils cause the immediate and at times often huge release of histamine and tryptase, amongst other mediators such as prostaglandins, leukotrienes, and chemokines. These can lead within minutes (to a maximum of 2 h) to local or more systemic manifestations including urticaria, vasodilatation, mucous secretion, smooth muscle contraction, influx of other inflammatory cells, as well as anaphylaxis with circulatory collapse.

In GI allergy, although manifestations may occur immediately, including those restricted to the GI tract, they are usually delayed (type IV) occurring hours to days after antigen exposure. Together with a lack of objective tests, this chronological "dissociation" adds significant complexity and delays to the diagnostic process and adds both uncertainty and suspicion towards a definitive diagnosis. Careful history and examination are key in the diagnosis of GI allergy. In a study of 437 children with food protein-induced gastrointestinal allergies, Meyer et al. found that the majority (67.7 %) of children had an atopic family history and 41.5 % had atopic dermatitis at an early age [10], emphasizing the careful documentation of such aspects in clinical evaluation. Table 19.1 summarizes "red flags" that should alert clinicians to the presence of GI allergy.

Table 19.1 Possible "red flags" for the presence of gastrointestinal food allergy

• Personal history of atopic disease especially occurring early in life (under 6 months of age)
• Family history of atopic disease in parents or siblings
• Presenting symptoms and signs indicative of food allergy especially where there is a reproducible response to the elimination and reintroduction of the suspected food (including change from exclusive breast milk feeds to formula or mixed feeds
The following symptoms and signs may be consistent with food allergy especially in the presence of one or more of the above
• Food refusal or aversion
• Gastro-esophageal reflux
• Vomiting
• "Colic"
• Abdominal pain
• Loose or frequent stools
• Constipation
• Perianal redness
• Blood and/or mucus in the stool
• Faltering growth
• Pruritis of the skin ± erythema
• Atopic eczema

Link with Motility Disorders: Overview and Putative Mechanisms

A study by Meyer et al. in 437 children with food allergy diagnosed by food elimination and rechallenge found that symptoms consistent with neuro-enteric disturbances were present in the majority, namely vomiting (57.8 %), back-arching and screaming (50 %), constipation (44.6 %), diarrhea (81 %), abdominal pain (89.9 %), and abdominal bloating (73.9 %). Rectal bleeding was seen in 38.5 % of patients [10]. The majority of patients were initially managed with a milk, soy, egg, and wheat-free diet (41.7 %) and at a median age of 8 years, 24.7 % of children still required to eliminate some of the food allergens suggesting that a proportion do not outgrow this allergic tendency.

Data in animal models of hypersensitivity reactions have shown that antigen challenge in vivo results in neurally mediated gastrointestinal dysmotility, including effects on the stomach (gastric emptying and secretion) [11] and small intestine (abolition of the migrating motor complex, increase in aborally propagating clustered contractions, and disruption of fasting and fed patterns) [12–15]. In sensitized animals with delayed gastric emptying, food antigen challenge showed histological evidence of mast cell degranulation in the gastric mucosa, increased intraluminal release of histamine, and increased markers specific for mucosal mast cell degranulation [16]. Furthermore, hypersensitivity to food proteins induced an increase in number and activation of mast cells and chronic motor alterations, such as intestinal hypermotility that seems to persist long after antigen challenge [17]. In sensitized rats, mucosal mast cells appear to mediate the motor responses induced by chronic oral exposure to ovalbumin [18]. Proteases from degranulated mast cells in close proximity to autonomic and enteric nerves cause acute and long-term hyperexcitability of ileal neurons in animal models by activating proteinase-activated receptor 2 (PAR2) on these neurons [19]. PAR2 has been suggested to play a role in nociceptive signaling, by sensitizing the vanilloid receptor 1 (TRVP1) to induce visceral hyperalgesia [20]. Exposure of mice to enteric-coated antigen promotes a T helper 2-associated eosinophilic inflammatory response that involves the esophagus, the stomach, and the small intestine and Peyer's patches and leads to the development of gastric dysmotility [21]. Furthermore, after oral ovalbumin challenge, allergic mice present higher levels of anxiety with increased activity in brain areas associated with emotional and affective behavior [22].

Although all the mechanisms by which food allergy induces disturbances in gut motility and sensation in patients are still poorly understood it is well known that allergic reactions to

food evoke immune inflammatory cell infiltration and activation at various gastrointestinal mucosal sites. Food allergy, either due to IgE- or non-IgE-mediated mechanisms, is commonly thought to elicit gut mucosa inflammation, where different types of immune cells (i.e., MCs, eosinophils, and T and B lymphocytes) are present and scattered along different sites of the gut [23]. Mast cells (MCs) are regarded as key effector cells of both immediate and delayed-type hypersensitivity reactions. Gastrointestinal MCs usually act either as effector cells secreting autocrine factors or facilitate the recruitment of other immunocompetent and inflammatory cells (i.e., eosinophils, lymphocytes, and neutrophils), which may in turn contribute to the persistence of allergic reactions [24]. On activation, MCs release a variety of bioactive substances, including vasoactive, nociceptive, and pro-inflammatory mediators, as well as neurotransmitters. Given their close proximity to enteric neurons, MC degranulation is capable of activating neural reflexes and muscle contractility leading to changes in gut motility [25, 26].

In both children and adults with irritable bowel syndrome (IBS), the average numbers of mucosal MCs have been shown to be increased at different intestinal sites, and to be in closer proximity to mucosal nerve endings compared to controls [27–29]. Not only were MCs found to release larger amounts of mediators such as histamine and tryptase, their spatial proximity to nerve fibers correlated with the severity of perceived abdominal pain in patients with IBS [30]. Eosinophils also have a recognized role in GI dysmotility [31].

Early Life Programming, Allergy, and Functional GI Disorders

It is increasingly recognized that early life events including inflammation, trauma, and stress may influence neuromuscular function and result in functional gastrointestinal disorders later in life [32]. For allergy this process is mainly implicated in abdominal pain and discussed further in the section of functional abdominal pain disorders.

Eosinophilic Esophagitis

Eosinophilic Esophagitis (EoE) is often considered an allergic condition given the nature of the inflammation seen with a predominance of allergy type cells, increased prevalence of a personal or family history of atopy, seasonal variation in symptoms in a proportion of cases suggesting a role for environmental allergens and response to allergen avoidance. Dysphagia and food impaction are common symptoms in older children with eosinophilic esophagitis (EoE) and represent the initial presenting symptoms in up to 20 % of cases [33]. Although both focal and diffuse esophageal anatomical abnormalities, including strictures, rings, or reduced organ caliber, might be responsible for generation of the symptoms, abnormalities in esophageal motility and distensibility are the most common causes [34–36].

By using the endo-FLIP (Functional Luminal Imaging Probe) system, which allows the assessment of the esophageal wall distensibility and hence of tissue remodeling and fibrosis, Nicodème et al. correlated in 70 symptomatic adult patients with EoE the esophageal distensibility with both susceptibility to food impaction and esophageal mucosal eosinophilia [37]. Reduced esophageal distensibility, which correlated with food impaction, was found in both patients with EoE and those with proton pump inhibitors-responsive EoE as compared to controls, whereas no correlation was found between esophageal distensibility and eosinophil mucosal infiltration. The authors suggested that reduced esophageal distensibility (<225 mm^2) in patients with EoE is predictive for food impaction and need for dilation. No such studies are available in pediatric age.

Wide ranges of esophageal motor abnormalities have been described in patients with EoE. Using conventional manometry, the esophageal motor pattern described includes normal peristalsis, complete aperistalsis, ineffective peristalsis secondary to simultaneous contractions, nutcracker esophagus, diffuse esophageal spasms, and achalasia. Nurko et al. found abnormalities in esophageal peristalsis in 41 % of children with EoE, including isolated and high-amplitude contractions and ineffective peristalsis both during fasting and during meals [38]. Notably, during the study all episodes of dysphagia correlated with abnormal esophageal peristaltic events. Similar motor abnormalities have been described also using high resolution manometry, although pan-esophageal pressurization seems to be the most consistent findings in EoE patients [39, 40].

In healthy individuals, both inner circular and outer longitudinal esophageal muscle layers are perfectly synchronous during peristalsis. Contraction of the longitudinal layer during deglutition is responsible for shortening of the esophagus, returning to its normal length when deglutition ends. By using simultaneously esophageal US and manometry, Korsapati et al. evaluated the interaction of circular and longitudinal muscle layers in patients with EoE and showed that the presence of asynchronicity between contractions of two muscle layers during peristalsis at the expense of longitudinal represents an abnormality that may contribute to the development of dysphagia [41].

The pathogenesis of esophageal motor abnormalities in EoE patients is still unknown. It is well documented that there is an eosinophilic infiltration in all esophageal layers. Studies in vitro have shown that eosinophils are capable to increase the contraction of the fibroblasts, and their degranulation is associated with axonal necrosis [21, 42, 43].

Moreover, eosinophil-derived major basic protein binds muscarinic acetylcholine receptors, which in turn can lead to smooth muscle contraction and subsequent dysmotility [44]. Mast cells may also play a role in the generation of esophageal

dysmotility. An increased number of MC in the esophageal mucosa as well as an upregulation of MC genes have been described in patients with EoE [45]. It is well known the effect of MC mediators on fibrogenesis as well as the effect on enteric neuromuscular function.

Gastro-esophageal Reflux Disease

Gastro-esophageal reflux disease (GERD) and cow's milk allergy (CMA) are both extremely common in infancy. Several studies emphasize a causal relationship between GERD and CMA at least in a subgroup of infants with GERD [46].

The prevalence of GERD attributable to CMA ranges between 16 and 56 %. Iacono et al. reported in 42 % of infants with GERD symptoms and histologic esophagitis the disappearance of reflux symptoms after they were put on a cow's milk free diet and the reappearance of symptoms on subsequent formula challenge [47]. Nielsen et al. showed that 56 % of children with severe GERD were found to have CMA on double-bind or open challenge [48]. Recently, Yukselen et al. identified food allergy in 65 of 151 (43 %) children with GERD refractory to medical therapy, and the majority of them (58/65, 89 %) were allergic to cow's milk, whilst only a small number (7/65, 11 %) to egg. Interestingly, the authors reported that only half of patients with GERD and food allergy had both positive oral challenge and skin prick test and/or specific IgE, whereas in the remaining half only the oral challenge confirmed the diagnosis of food allergy [49].

With the exception of those patients with mild typical CMA manifestations, such as atopic dermatitis, rhinitis, and diarrhea, it is challenging to discriminate between the symptoms observed in primary GERD and those of GERD associated with CMA. Early studies have advocated the role of pH monitoring to discriminate between primary GERD and that secondary to CMA. A particular phasic pH pattern characterized by a slow and progressive decrease in esophageal pH between two feeds was suggested as a sensitive and specific index for identifying patients with CMA-induced GERD [50, 51]. However, this finding has not been confirmed by subsequent studies [48, 52]. Nielsen and colleagues [48] performed 48-h pH monitoring in ten children with severe GERD and CMA, with cow's milk elimination diet at day 1 and cow's milk challenge at day 2. Although the authors showed that children with GERD and CMA had more abnormal pH monitoring than those without the association, they failed to find any differences in the reflux index between the two recording days. By using impedance-pH monitoring, which allows detection of acid, weakly acidic and weakly alkaline reflux, Borrelli et al. found in a subgroup of infants and children with CMA and GERD that cow's milk challenge increases the number of weakly acidic reflux episodes suggesting that a challenge during 48 h impedance-pH monitoring might increases the yield in identifying this subgroup of patients [53].

The mechanisms by which food allergy induces GER are still poorly understood. Data in animal models of immediate-type hypersensitivity reactions have shown that antigen challenge in vivo results in neurally mediated foregut dysmotility, such as delayed gastric emptying. Ravelli et al. showed that milk challenge induces gastric electrical dysrhythmias and delayed gastric emptying in infants with vomiting due to CMA [54]. Schäppi et al. showed that early-onset neuroimmune interactions induced by cow's milk challenge in the gastric mucosa of atopic children are associated with rapid derangement of gastric myoelectrical activity [55]. Notably, in this study, cow's milk challenge induced rapid degranulation of mast cells and eosinophils. Activated mast cells were closely associated with mucosal nerve fibers, and released mast cell tryptase was co-localized with proteinase activated receptors 2 (PAR-2) on mucosal nerve fibers. In the same timeframe as these morphological changes occurred, there was a rapid (within 2 min) induction of electrogastrographic myoelectrical abnormalities. Intriguingly, in experimental animals, gastric activation of PAR-2 induces neurally mediated motor and secretory responses represented by a fundic biphasic contractile response, which involves relaxation followed by contraction, and suppression of acid production [56, 57]. Furthermore, it has been shown that a reduced prevalence of normal electrical rhythm and an increased rate of episodes of dysrhythmia are associated with antral hypo-contractility, which in turn leads to a gastric emptying delay [58, 59].

Delayed gastric emptying may increase GER by increasing the availability of material to reflux or by inducing prolonged gastric distention and more transient lower esophageal sphincter relaxations (TLESR). Simultaneous esophageal manometry and gastric emptying breath tests in healthy adults and premature infants showed a moderate but significant correlation between gastric emptying delay and rate of postprandial TLESRs [60, 61]. Moreover, using simultaneous gastric emptying and pH-MII, Sifrim and colleagues showed that the slower the gastric emptying, the higher the pH and proximal extent of the reflux episodes [62]. Furthermore, it is well known that nonacid reflux episodes are more likely to occur during feeding and during the first postprandial hours, with greater frequency in infants compared with older children. Thus, it could be hypothesized that neuroimmune interactions induced during cow's milk challenge by activating gastric PAR2 suppress the acid gastric production and deranges the gastric motor activity, which in turn delay the gastric emptying and increase the rate of TLESRs, resulting in an increase in the number of nonacid reflux episodes.

The high prevalence of the GERD-CMA association might be explained by different diagnostic modalities used

for GERD, including endoscopy, histology, and esophageal pH monitoring, as well as different diagnostic criteria for cow milk protein allergy. However, being this association far beyond what can be expected from pure coexistence of the two entities, it should induce pediatricians to screen for possible concomitant CMA mainly in those infants and children with GERD unresponsive to medical treatment [63].

Infantile Colic

Infantile colic (IC) describes a symptom complex of excessive and inconsolable crying in babies that otherwise appear to be healthy and thriving. Although implied in its name, the exact focus or nature of colic is not known. It classically develops in the first 2–4 weeks of life and persists through to the third or fourth month of age, affecting between 15 and 40 % of infants [6]. The impact of IC can be considerable and therefore, although the natural history is of gradual resolution without harmful consequences, many parents and physicians have sought causative factors and interventions to try and alleviate the symptoms (see Chap. 34). Allergy is one such factor.

The association between IC and allergic disorders has long been suggested mainly through three bodies of evidence, namely, response of IC to dietary exclusion, predisposition of IC to atopic conditions, and potential similarities in disturbances of neuro-enteric function and microbiome between IC and food allergy [64]. A large number of studies have investigated the response of IC to dietary exclusion either through the use of maternal exclusion of dietary antigens whilst breastfeeding or use of specialized milk formulae. Although some studies have shown no differences in prevalence of IC between breast-fed and bottle-fed infants [6, 65–67], or any significant improvement in cry duration in breast-fed infants with IC in whom mothers have eliminated cow's milk protein [68], others have suggested that maternal exclusion of cow's milk protein or indeed a broader exclusion is beneficial [69, 70].

Hill et al. explored an extensive maternal exclusion of allergens (excluding cows milk protein, eggs, wheat, soya, peanuts, tree nuts, and fish) in breast-fed babies with IC and reported a significant response rate (defined as ≥ 25 % reduction in cry/fuss duration; 74 % vs. 37 %) and reduction in infant crying duration in the intervention group compared to controls [70]. In formula fed infants, Iacono et al. showed improvement or complete resolution in 50 of 70 infants with diagnosed severe IC and put onto cow's milk protein exclusion (Soya milk formula). Upon rechallenge with cow's milk protein-containing formula all 50 infants relapsed and then again showed remission with exclusion [71]. More recently, the use of soy-based milks in infants under 6 months of age has fallen out of favor given concerns over their content of phytoestrogens with potential adverse effects [72]. A number of studies have looked at excluding cow's milk protein with the use of extensively hydrolysed formulae. In a randomized, double-blind, parallel trial Lucassen studied 43 healthy, thriving formula-fed infants with IC (<6 months old, crying >3 h per day on at least 3 days per week). The infants were randomized to receive either a whey hydrolysate formula ($n=23$) or standard formula ($n=20$) and the difference in the duration of crying (minutes per day) compared between the qualification week and intervention week. Analysis (intention to treat) found that the whey hydrolysate group showed a mean decrease in crying duration of 63 min per day. The study characteristics, however, did not allow significant differences to be determined [73]. Variable improvements have also been reported in other studies using dietary modification in including the use of extensively hydrolysed cow's milk formulae [74–76].

Further association between IC and food allergy is perhaps supported by longitudinal studies on infantile colic [65, 71, 77]. Savino et al. carried out a prospective study on 103 infants aged 31–87 days who were then recalled after 10 years and evaluated. Not only did colic appear to predispose to recurrent abdominal pain ($p=0.001$) but there was an association with the development of allergic disorders including atopic eczema and food allergy ($p<0.05$). Furthermore, a family history of gastrointestinal diseases and atopic diseases was significantly more prevalent in infants with colic than in controls ($p<0.05$) [78]. It is, however, unclear whether there were any elements of recall bias in these studies. Further, more robust studies are needed to understand this association or indeed whether IC captures a population of allergic children that could be identified earlier in life.

It is possible that allergy, through its immune-mediated pathways, initiates changes within the function of the enteric nerves (dysmotility and visceral hypersensitivity) or is associated with alterations in the microbiome. The putative mechanisms are well described within this chapter and later in the book. There are, of course, considerable ethical issues with advocating or justifying research or indeed routine interventional assessment (e.g., endoscopy) in children with IC in the absence of any red flags for organic disease. Alterations in the microbiome and putative effects of these on the enteric nerve network and function are increasingly reported in recurrent abdominal pain. Although dysbiosis is similarly described in both food allergy and infantile colic in children [79, 80], the exact mechanisms and effects of these are unclear. There is evidence, however, that altering the microbiota population with the use of probiotics may have an impact on IC [81].

In conclusion, there remains considerable debate on whether the literature to date conclusively confirms an association between IC and food allergy given that the quality of the published studies has been poor with issues around study

design, disease definition, and consistency of interventions with dietary modification. Furthermore, it is unclear whether any reported effects of dietary manipulation relate to true immune-mediated allergy or merely reflect issues around tolerance of ingested foods (osmolality, protein quality) or effects on gastrointestinal motility [82]. Overall, current estimates suggest that cow's milk allergy is present in only 2–5 % of babies with colic [83] (see Chap. 34). The new Rome IV guidelines state that there is inadequate evidence to support the routine elimination of allergens such as cow's milk protein for the treatment of IC [84]. It remains possible that a small subset of children with IC, especially those with red flags of allergy (Table 19.1), may derive potential benefit from dietary manipulation, however this must be balanced against the natural history of improvement, nutritional adequacy in mothers and infants as well as the risk, conversely, of compounding the development of food allergy arising from loss of tolerance due to allergen avoidance [85].

Functional Abdominal Pain Disorders

Recurrent abdominal pain (RAP) is a common complaint in children and subclassified in the recently published Rome IV criteria, into four functional abdominal pain disorders (FAPD), including functional dyspepsia (FD), irritable bowel syndrome (IBS), abdominal migraine, and FAPD—not otherwise specified [84, 86] (see Chaps. 35, 36, 38, and 42). Although there may be variability in predominant regions of the GI tract involved FAPDs seem to share common pathogenic mechanisms of visceral hypersensitivity and central hypervigilance, which appear to result from disruption of the microbiota-gut-brain axis and abnormal enteric neuroimmune interactions.

As we broach the question of whether there is an association between FAPDs and allergy, a number of similarities between the two conditions become apparent. Not only are the symptom complexes similar between the two disorders with a predominance of abnormalities in sensation and motility, the key immune cells implicated in both disorders show considerable overlap, namely T cells, mast cells, and eosinophils [10, 87, 88]. The pathophysiology of FAPDs such as IBS has been extensively studied in adults and, more recently, in children [29, 89] with the most consistent finding of an increased numbers of mast cells sitting in close apposition to nerve fibers in the gut mucosa as part of a low-grade inflammation. In adults, jejunal biopsies of IBS-D patients exhibit increased mast cell counts and evidence of their activation, which correlates with clinical symptoms [90]. Mast cells have also been implicated in functional dyspepsia [31]. Faure et al. analyzed the inflammatory cells in the colonic and gastric mucosa of children with functional dyspepsia or IBS. Eleven of 12 patients with IBS and 9 of 17 patients with FD had evidence of mostly low-grade inflammation of the intestinal mucosa [91]. Another study noted that 71 % of children evaluated for suspected functional dyspepsia had duodenal eosinophilia (>10 eosinophils per high-power field of view) [92]. The real clinical significance and link to allergy, however, remains unclear.

In one of the earliest studies to explore the potential association between recurrent abdominal pain in children and allergy, Kokkonen et al. examined a consecutive series of 84 children (43 males, 41 females, mean age 7.9 years) referred with recurrent abdominal pain over a period of 1 year. All patients underwent gastro-duodenoscopy and biopsy. Based on an open elimination-challenge test, a considerable proportion (33 %) of subjects was diagnosed with food allergy, showing a close relationship with duodenal lesions namely mild elevations in the numbers of eosinophils [93]. The findings of this study, however, were probably reflective of a degree of referral bias given that in a subsequent community-based study in 404 children the same researchers found evidence of milk intolerance in only 9 subjects out of 64 with recurrent abdominal pain [94].

In an open label study of gastric mucosal cow's milk challenge in 10 atopic (personal and/or family history) and 6 nonatopic children (ages 2–12 years) investigated consecutively with symptoms of functional dyspepsia. Simultaneous endoscopy, surface electrogastrography, and milk challenge were undertaken and laser scanning fluorescence microscopy used to examine the association of mast cell tryptase with mucosal nerves in the gastric mucosa before and after challenge. Eosinophils and mast cells within the lamina propria were increased in number in children with atopic functional dyspepsia and degranulated rapidly after cow's milk challenge in the atopic group. Mast cells were closely associated with mucosal nerve fibers and released tryptase, which colocalised with proteinase-activated receptors on mucosal nerve fibers. The gastric antral slow wave became abnormal within 2 min of antigen challenge in atopic children showing a decrease in the normal myoelectrical rhythm paralleling an increase in bradygastria ($P < 0.01$). The study, however, was small and timing of the reaction unclear as how it relates to the broader group of FAPDs [55].

Part of the current challenge is that many patients with FAPD report and consider their symptoms to be related to meals [95] and similarly not all responses to diet are likely to represent true allergy given reported "reactions" by parents in almost 15 %. In adult studies almost a third of patients with IBS report the onset or worsening of symptoms after meals (28 % within 15 min and 93 % within 3 h) [96, 97]. Even though in some studies adult and pediatric patients with IBS have been reported to have a higher incidence of atopy [98], it has been difficult to confirm that this food-related association is due to allergy especially given the timing of the response appears to favor an immediate hypersensitivity

mechanism, which is not the predominant form seen in GI allergy. Furthermore, a placebo response of up to 50 % is recognized in children and adults with FAPDs [99]. However, a recent review of the IBS literature found a significant number of studies, including in children, reporting an association between atopy (including food allergy and asthma) and IBS. The authors suggest that the "concept of food allergy should be included as a possible cause of IBS, and a dietary approach may have a place in the routine clinical management of IBS" [100]. Certainly there is emerging evidence of the value of specialized diets in the management of children with FAPDs, including low FODMAP diets [101]. The exact mechanisms, nutritional sufficiency and safety of such restrictive diets in children have not been confirmed and should be approached with caution until better clarification is achieved.

Some efficacy of treatments used in allergy such as antihistamines and mast cell stabilizers has been reported although again it is unclear whether this is a true effect on decreasing allergic inflammation or indeed exerting a placebo response [88, 102]. Perhaps most interestingly and a possible explanation for the absence of overt inflammation in many children with FAPDs and suspected food allergy despite clear changes in nerve function is the concept of programming of such function earlier in life perhaps at a time of a more significant inflammatory response. It is increasingly recognized that early life events including gastrointestinal inflammation, trauma, and stress may result in maladaptive responses that could lead to the development of chronic pain conditions such as FGIDs [32]. In a study of 52 subjects diagnosed with CMA in the first year of life (mean age 8.1 ± 4.48 years, 62 % girls) and 53 controls (mean age 9.7 ± 4.20 years, 55 % girls), Saps et al. found a much higher proportion (44.2 %) of subjects who reported GI symptoms which included abdominal pain, constipation, or diarrhea compared with only 20.7 % of controls (odds ratio 3.03, $P = 0.01$). Abdominal pain was significantly more common in cases (30.8 %) versus controls (9.4 %) (odds ratio 4.27 [1.43–12.7]). They concluded that CMA in the first year of life constituted a risk factor for the development of FGIDs in children many years later. Saps et al. [103] and Olen et al. [104] confirmed this association, finding that children with a personal history of allergy-related diseases (asthma, allergic rhinitis, eczema, and food hypersensitivity) earlier in life were more prone to have abdominal pain at 12 year of age. An association with abdominal pain was also present when considering food allergy alone, but only for children who presented it at the age of 8 years. The risk of having IBS appeared to be increased amongst subjects reporting intolerance to a higher number of foods [105]. In the study from Lillestøl et al. [106], atopic patients had increased intestinal permeability and density of IgE-bearing cells compared with non-atopic patients, but gastrointestinal symptoms did not differ between groups. These partially conflicting data may suggest that further studies are needed to assess the long-term role of early allergy in developing functional abdominal pain. More recently, Tan et al. evaluated 11,242 children (age range: 7–18 years) with IBS and 44,968 age- and sex-matched control subjects who had been examined between 2000 and 2008 showing that children with antecedent allergic diseases had a greater risk of IBS than controls ($p < 0.001$) [107]. Such early life programming has now been implicated in a number of scenarios including post-infectious irritable bowel syndrome [32].

Constipation

Several studies have suggested that cow's milk free diet or more restricted diets can be effective at least in a subgroup of patients with functional constipation unresponsive to stool softeners. However, the causal relationship between CMA and chronic constipation is highly debated.

Since the first report in 1978 from Buisseret, who first suggested that CMA was an underestimated caused of constipation, several studies have focus on the association between the two entities, showing a rate of successful outcome of the hypoallergenic diet in children with unresponsive constipation and suspected or confirmed food allergy ranging between 28 and 78 % [108]. In 1995, Iacono et al. showed in the first open label study that 21 out of 27 children with chronic constipation unresponsive to stool softeners did respond to a cow's milk protein-free diet [109]. The same group, in a later double-blind cross-over study, showed that 44 of the 65 children (68 %) with chronic constipation unresponsive to lactulose significantly improved when cow's milk was replaced by soy milk, whereas none of the children on cow's milk showed any response [110]. All 44 children who responded to the CM-free diet relapsed on subsequent double-bind placebo-controlled challenge. Similarly, other studies have suggested that food allergies may be the underlying cause at least in a subgroup of children with refractory chronic constipation [111, 112]. Recently, in an open-label study Irastorza et al. found that 27 of 69 children (39 %) responded to 3-week period of CM-free diet; the symptom reappeared after the reintroduction of cow's milk in the diet [113]. Similarly, El Hodhod et al. showed an improvement after CM-free diet in high percentage (78 %) of children with chronic constipation [114]. In a large prospective observational study, Kiefte-de Jong et al. showed that although no correlation was found between constipation and the timing of introduction of common food allergens, a history of cow's milk allergy in the first year of life was significantly associated with functional constipation in childhood (OR: 1.57; 95 % CI: 1.04–2.36) [115]. Finally, Syrigou et al. studied 44 children aged between 6 months and 14 years (median 42 months) with intractable chronic constipation, and by using

atopy patch test (APT) they found that 32 had positive APT (15 were positive to one; six, to two and 11 to three or more food allergens, wheat and egg being the most common). Interestingly, constipation improved in 28/32 children after withdrawing the APT-positive foods for an 8-week period, and there was a relapse of constipation after an oral food challenge [116].

On the other hand, other studies did not find significant difference in the prevalence of food allergy between constipated children and controls. For instance, Loening-Baucke found a very low prevalence (2 %) of food allergy in over 185 children less than 2 years of age presenting with functional constipation [117]. Similarly, other studies have not shown significant difference in the prevalence of constipation between allergic children and controls [103, 118, 119]. Therefore, the causal relationship between food allergy and constipation is not universally accepted.

The mechanisms by which food allergy induces constipation are still poorly understood. Several studies in children with chronic constipation related to CMA have shown a marked eosinophils and lymphocytes infiltration in the rectal lamina propria, which regressed during elimination diet [110–112]. In children with chronic constipation related to food allergy, Borrelli et al. showed an increase both in the density of rectal mucosa mast MC and in the number of MC in close proximity to submucosal rectal nerve endings [120]. Remarkably, the restricted diet was effective in reducing MC mucosal infiltration and normalizing the MC–nerve interactions supporting the hypothesis that the increase in MCs infiltration and the relationship between inflammatory cells and mucosal nerve fibers was food-allergen dependent [120]. The presence of an increased number of eosinophils and MC in the rectal lamina propria and their close spatial relationship with submucosal nerve endings has been suggested as being of functional significance in affecting neuromuscular function. By using physiology tests, such as anorectal manometry and radiopaque markers study for colonic transit time, studies in the children with chronic constipation related to food allergy have reported both prolonged colonic transit time and abnormalities in anorectal motility, such as an increased anal resting pressure and an abnormal relaxation of the anal canal upon balloon distension [121, 122]. These features tended to normalize or disappear on elimination diet. Borrelli et al. showed that anal resting pressure correlated significantly both with density of rectal MC infiltration and with spatial vicinity of MC to submucosal rectal nerve fibers, whereas the latter were inversely correlated with the degree of anal relaxation upon rectal distension, suggesting that an increase of MCs and eosinophils and their mediators may be contributing to anorectal motor abnormalities in children with food allergy-related chronic constipation [120]. However, studies addressing the mechanisms through which the "allergic" inflammation affect anorectal and colonic motor activity and how the diet can influence the relationship between inflammatory cells and colonic/anorectal neuromuscular function are undoubtedly advocated.

Although the causal relationship between food allergy and constipation is not universally accepted, the current ESPGHAN-NASPGHAN guidelines regarding the management and treatment of constipation suggest to consider an hypo-allergic formula for 2–4 weeks in infants with functional constipation resistant to treatment [123].

Conclusion

There is no doubt that GI allergy and neurogastroenterology are intertwined across a number of aspects, which has driven an enormous body of research, literature, and attempts to translate findings into clinical practice. It is likely that many of the common GI conditions discussed above will include a subgroup of children with GI allergy who may benefit from appropriate management. There remain a number of challenges that need to be addressed including clarification over the specific patients that should be targeted, the optimal approach and timing for the short- and long-term management of such cases and how outcomes should be best assessed. This is compounded by the possibility that in many children the gastrointestinal symptoms and signs are a result of programming earlier in life and unlikely to truly respond to interventions designed to alleviate active inflammation. One hopes that the coming years will bring clarity over many of these aspects. Overall, clinicians treating gastrointestinal conditions in children need not only to have an awareness of GI allergy and expertise to identify and treat affected patients but this must be balanced with caution over the real need of interventions and their severity, avoiding the blunderbuss treatment of all children with the hope that some will respond.

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Swallowing and Oropharyngeal Disorders

20

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Swallowing and Oropharyngeal Disorders

Swallowing disorders have become increasingly recognized in recent years as more premature infants and medically complex children are living longer and presenting to medical attention [1, 2]. These conditions present in a wide variety of ways and can result from a combination of developmental, neurologic, and anatomic issues, each of which requires an individualized approach to treatment and these patients are frequently diagnosed and managed by general providers in addition to motility and aerodigestive specialists. The purpose of this discussion is to review the etiology, differential diagnosis, and therapies for swallowing dysfunction in the pediatric population. Assessment and techniques for studying swallowing and oropharyngeal disorders are discussed and addressed in Chap. 7.

Although occurring many times throughout the day without any apparent effort for most healthy children, the process of swallowing requires carefully orchestrated coordination from a large array of muscles and nerves in the mouth, pharynx, and esophagus, all mediated by the central nervous system. The act of swallowing can be divided into several key phases and a failure in any of the requisite components can lead to swallowing dysfunction and resultant aspiration [2, 3]. Temporal coordination of these processes is especially important for survival since both breathing and swallowing share the same common pathway by way of the pharynx [3].

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The mechanistic phases of swallowing or deglutition include the preparatory, oral, pharyngeal, and esophageal phases. Each of these elements will be discussed in turn.

In the first or oral preparatory phase the food is taken into the mouth, chewed and prepared as a bolus that is held between the tongue and the hard palate in preparation for the next phase. In the second or oral phase food is moved from the mouth into the pharynx by means of carefully orchestrated movements that include propulsion of food into the oropharynx by the tongue in concert with elevation of the soft palate to prevent food entry into the nasopharynx.

In the third or pharyngeal phase, the food bolus must pass through the pharynx into the esophagus while the airway is adequately protected and therefore requires mechanical closure of the vocal folds and rising of the larynx while the pharyngeal muscles in sync with the base of the tongue move the bolus past a relaxed upper esophageal sphincter. In the last or esophageal phase the bolus moves through the esophagus by means of coordinated involuntary contractions that propel the bolus from proximal to distal esophagus and into the stomach.

The first two phases of swallowing, the preparatory and oral phases, are importantly under voluntary control in children and adults but are involuntary in infants. During the newborn period the sucking reflex is regulated by the central nervous system at the brain stem. The transition to the voluntary pattern of oral and pharyngeal phases occurs around 6 months of age when infants transition from reflexive sucking from a nipple to being able to appropriately handle solid foods in the oropharynx.

As discussed above, the complex act of swallowing requires fine-tuned coordination between a wide array of neural reflexes combined with active muscular effort and each of these components must mature as a child develops. Dysfunction can therefore occur at multiple levels in this intricate process and an appropriate understanding of the possible structural, anatomic, and neurologic abnormalities that can disrupt this process enables providers to take a thoughtful approach to the evaluation and treatment of pediatric dysphagia.

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Increasing Incidence of Swallowing Disorders

Swallowing disorders are common and studies have shown that their incidence is increasing in the pediatric population, likely due to a combination of greater recognition of the importance of these disorders, improved diagnostic tools, and greatly improved survival rates of premature infants [4]. Not only do sicker and more preterm infants have delayed development of mature swallow function as a result of neurodevelopmental delay, they are also more likely to have chronic lung disease and in some cases other congenital anomalies, which also contribute to dysfunctional feeding. Feeding difficulties not only affect infants while still in the neonatal intensive care unit and often prolong their hospital stay but are also more likely to be long-lasting and require active management as the infants continue to develop [1]. In a study by Hawdon et al., preterm infants with abnormal feeding assessments at term were found to have ongoing significant difficulty with solids at 6 months and 12 months of age [1].

The overall prevalence of oropharyngeal dysphagia is not well known but is likely more common that previously appreciated. Estimates of feeding disorder prevalence range from 25 to 45 % in the general pediatric population and 33 to 80 % in the developmentally delayed population [5]. The Centers for Disease Control and Prevention reported in 2010 that 2.6 % of sick infants discharged from short hospital stays had feeding disorders [6]. What percentage of these feeding disorders are swallowing related is not known but increased recognition of these disorders suggests that the proportion is high. Recognition is important as they contribute to longer hospital stays and increased mortality [7]. A key point of all of these studies is an emphasis on earlier diagnosis so that feeding difficulties can be addressed earlier and before they become established patterns that can increase morbidity and mortality. Even with increased recognition, however, many children are still not diagnosed and treated adequately before some degree of permanent lung damage has occurred [8].

Presentation of Swallowing Disorders

The clinical presentation of swallowing disorders can be subtle and often is nonspecific and so providers must maintain a low threshold for considering swallowing dysfunction as playing a contributing or central role for any given patient with respiratory symptoms or feeding problems [9]. Overt symptoms of aspiration include gagging, choking, coughing, bradycardia, apnea, or cyanosis with feeds but less obvious symptoms include subtle findings like irritability or fussiness around feeds, noisy or wet breathing after feeding, arching during feeding, or signs such as delayed swallowing, voice changes, tearing, nasal congestion, wheezing, or facial redness [3, 10]. It is important to notice that all of the symptoms of aspiration have also been attributed to gastroesophageal reflux disease [11] and many patients are incorrectly diagnosed with GERD rather than aspiration. Making the correct diagnosis is critical because the treatments are different and the risk of missing the diagnosis could result in significant morbidity (Table 20.1).

Weir et al. performed a retrospective study in which they compared 11 clinical markers of dysphagia with results of videofluoroscopic swallow studies in 150 children. The authors found that wet voice, wet breathing, and cough were reliable clinical markers for and significantly associated with aspiration of thin liquids but there were no good markers for aspiration of purees or for other types of swallowing dysfunction such as laryngeal penetration suggesting that any patient with persistent symptoms should undergo a clinical feeding evaluation or videofluoroscopic study because history alone is not adequate [10].

In most children, the laryngeal cough reflex serves as a protective mechanism by which mechanoreceptors and chemoreceptors in the hypopharynx trigger a cough when irritated by aspirated material [12]. It is as a result of these signaling pathways that patients, parents, and providers are able to discern some of the symptoms of overt aspiration. Some groups have found that signs and symptoms vary by age, perhaps as a result of differential airway responses to aspiration, such that infants tend to exhibit apnea, vocal cord constriction, rapid swallowing, and bradycardia as a result of laryngeal chemoreflexes while older children tend to have cough [3, 10, 13]. This is thought to be due to development of higher level central neural processing in adults as opposed to changes in the chemoreceptors in the larynx [13]. Newman et al. showed that children also exhibit a different pattern for clearing laryngeal penetration. In contrast to adults, who must cough to clear the material, children with laryngeal penetration were able to clear the area with additional swallows [14].

While chemoreceptors and mechanoreceptors may exist in the pediatric airway, a significant proportion of aspiration in children is silent. It has been suggested that silent aspiration

Table 20.1 Clinical presentation of swallowing disorders

Signs and symptoms
• Coughing, choking, gagging with or after feeds
• Wheezing, noisy or wet breathing
• Blue spells, apneas, bradycardias
• Feeding refusal, arching during feeds
• Voice changes
• Tearing and red eyes
• Nasal congestion
• Recurrent pneumonia
Mimickers of swallowing disorders
• Gastroesophageal reflux
• Esophageal stasis from dysmotility (esophageal atresia, achalasia)

results from dysregulation of the laryngeal cough reflex in addition to weakness or incoordination of the pharyngeal musculature and inability to produce a cough [15]. Studies by Weir et al. have revealed that silent aspiration is quite common in children with feeding difficulties and especially those with neurologic disorders and developmental delay. In their prospective cohort, Weir found that in the 34 % of patients with dysphagia in their study had silent aspiration [12]. In another cohort, silent aspiration was observed in as many as 94 % of patients [16]. These rates of silent aspiration in children are much higher than rates in adults [12]. This high rate of silent aspiration lowers the value of the clinical feeding evaluation and thus empowers the clinician to order a swallowing study based on clinical suspicion rather than symptoms during feeding alone.

Because the majority of aspiration is silent, these children are often misdiagnosed as having gastroesophageal reflux disease as the symptoms are identical [17–19] and include with gagging, choking, coughing, and blue spells in infants and children [20]. Making the correct diagnosis is critical to avoid unnecessary therapies because, although thickening of feeds might be effective in the treatment of reflux, acid blockade is not sufficient treatment for oropharyngeal aspiration.

Causes of Oropharyngeal Dysphagia

The differential for swallowing disorders and aspiration includes developmental issues, neurologic conditions, and anatomic abnormalities. Rommel et al. differentiated swallowing disorders into the categories of medical, oral, and behavioral and emphasized the importance of considering the contribution of each of these elements in diagnosing and managing swallow dysfunction [21]. Regardless of the underlying trigger for swallowing disorders, secondary behavioral feeding disorders are common; Burklow et al. identified factors related to dysphagia in 103 children and found that in 80 % of cases there was a behavioral component to the complex feeding problem [22]. Therefore, multifactorial approaches to feeding disorders are needed. The following discussion will focus on the three main categories of swallowing dysfunction: developmental abnormalities, neurologic abnormalities, and anatomic abnormalities (Table 20.2).

Table 20.2 Differential diagnosis of aspiration

Developmental
• Prematurity
• Neonatal swallowing dysfunction
Neurologic
• Chiari malformation
• Cerebral palsy
• Other neuromuscular disorders
Anatomic
• Laryngeal cleft
• Vocal cord paralysis
• Tracheoesophageal fistula
Other
• Upper esophageal sphincter dysfunction, enlarged tonsils, tongue-tie, submucosal cleft palate, esophagitis

Developmental Disorders

Swallowing development starts at 10–14 weeks of gestation. Sucking behavior develops initially between 18 and 24 weeks of gestation and in premature infants continues to develop up to 36 weeks postmenstrual age. In most cases by 34 weeks premature infants are capable of coordinated oral feeding but even typically developing full term infants have improvement in coordination of feeding over time [23]. As premature infants develop many continue to have issues with oropharyngeal dysphagia, however with up to 70 % of very low birth weight infants showing swallowing abnormalities and up to 30 % are not sufficiently protecting their airway to prevent aspiration [23, 24].

When a neonate has swallowing dysfunction by videofluoroscopic swallow study, with normal upper airway and with no major associated neurological, anatomic, or craniofacial abnormalities at the time of presentation, they are given the diagnosis of neonatal swallowing dysfunction though the dysfunction can persist through the first 2 years of life. Infants born premature or with low birth weight (below the tenth percentile) are at increased risk for swallowing problems and a gestational age of 34 weeks is considered critical for the development of appropriate swallow function [21]. Deglutition is commonly considered one of the most complex reflex neural activities for all humans and for infants in particular it is one of the most intricate acts they must perform safely in order to survive and grow [23].

The exact etiology of neonatal swallowing dysfunction is poorly understood but these conditions are most likely multifactorial and due to delayed development of the reflexes and neuromuscular coordination needed for safe swallowing. Contributors to swallowing dysfunction in premature infants include prolonged respiratory cessation (up to 4 s compared to 1 s in adults) and inward as opposed to protective outward airflow in the pharynx around the period of swallowing [3]. There are some studies in mice that suggest that developmental swallowing disorders might be due to altered hindbrain patterning during prenatal development [25].

Fortunately, the prognosis is good for patients with developmental swallowing dysfunction. Most infants show improvement in swallow study results within 3-4 months from their first study and will have resolution of their swallowing dysfunction within 1 year of starting feeding therapy [26, 27].

From studies of diagnostic testing, the rate of abnormal swallow tests in children decreases significantly with time such that an abnormal assessment of swallow function beyond the age of 2 years warrants further evaluation.

The therapeutic consequence of this encouraging natural history are great; the goal in patients with neonatal swallowing dysfunction to determine the safest method of feeding (NG, thickened oral feeds) to buy time, avoid placing a permanent feeding tube (gastrostomy), and await resolution of the swallowing dysfunction. In a single study comparing outcomes of children with swallowing dysfunction who received gastrostomy tube feeding compared to patients given thickened feeds, those who continued with oral feeds had improved outcomes compared to patients that received gastrostomy tube feeds [28]. This study, combined with the natural history of improved swallow function over time, supports a noninvasive approach to these patients.

Neurologic Disorders

The central and peripheral nervous systems are both essential for coordinated, effective, and safe swallow function in all age groups. Swallow dysfunction can result from issues with the muscles, nerves, and receptors of the pharynx in addition to problems in the spinal cord, brainstem, and other regions of the brain. Peripheral neuromuscular disorders typically cause a combination of low muscle tone in addition to poor coordination of the stages of swallowing and decreased ability to clear the airway [3]. Central nervous system insults include conditions such as cerebral palsy, Arnold-Chiari malformations, and cerebral vascular accidents [2].

In children with persistent aspiration beyond the age of 2 years who show no improvement in swallowing function merit further evaluation which often included magnetic resonance imaging of the brain to evaluate for a Chiari malformation. Up to 20 % of patients with Chiari malformations have been found to have aspiration and in these patients the dysphagia is often progressive as a result of compression of the brainstem and cranial nerves by low-lying cerebellar tonsils [29]. Type 1 Chiari malformation is more likely in these cases that are diagnosed as a result of dysphagia since type 2 malformations usually have other associated malformations such as spinal dysraphism that typically lead to earlier diagnosis [29, 30]. In a small pediatric case series of patients with Chiari malformations, there was significant UES dysfunction which resulted in dysphagia and aspiration risk which completely resolved after surgical repair [31]. Fortunately, the prognosis is good for these patients after surgical repair.

Cerebral palsy is also associated with a high proportion of children having dysphagia. This condition is becoming a more common neurologic cause of swallow dysfunction as the survival rate of extreme premature infants has increased. It is also important to note that although cerebral palsy is a static central neurologic condition, swallow function in these patients can worsen over time and must be monitored closely [3]. Risk factors for worsening dysfunction may include infections, hypothyroidism, seizure disorders, and medication effects, among others.

Anatomic Abnormalities

Pathologic conditions at any of the sites along the aerodigestive tract can negatively affect swallow function and lead to oropharyngeal dysphagia. Anatomic abnormalities that can cause aspiration include defects in the nasopharynx, oropharynx, larynx, esophagus, and trachea.

Obstruction in the nasopharynx typically impairs breathing, which in young infants can cause dyscoordination of the oral and pharyngeal swallow phases. Choanal atresia is the most severe form of nasal obstruction but a similar end result can also be seen with other conditions including allergic rhinitis, adenoid hypertrophy, or congenital masses of the nasopharynx [2]. These lesions can lead to aspiration, slow eating, and aversion to textures. While it is beyond the scope of this chapter, palatal abnormalities (cleft palate, submucosal cleft palate, asymmetrical palate movement) can lead to nasal reflux, aspiration, and food avoidance. Exam of the palate is critical in children with chronic nasal congestion, ineffective suck, recurrent sinus disease, and nasal voice quality.

From a laryngeal perspective, the biggest diagnosis to rule out in patients with persistent or severe aspiration is a laryngeal cleft. Laryngeal clefts were once felt to be a rare congenital malformations but more recent studies suggest this is a more common cause of aspiration than originally thought [32]. This anomaly occurs in 1 in 10–20,000 live births and is thought to result from the failure of fusion of the tracheoesophageal septum. The diagnosis of laryngeal cleft can only be made by direct laryngoscopy under anesthesia. Laryngoscopy can determine the extent of the defect, ranging from type 1, which is a supraglottic interarytenoid defect in which the cleft lies above the level of the posterior cricoid cartilage, to type 4, in which the cleft extends as far down as the thoracic trachea. The management of these anomalies ranges from conservative medical management for type 1 if the patient is minimally symptomatic to surgical approaches that are now performed endoscopically [33]. It is important to know, however, that even when these laryngeal clefts are repaired, 23 % of patients continue to have aspiration, even after repair, suggesting that the swallowing dysfunction, even with patients with anatomic abnormalities, is multifactorial [34].

Vocal cord paralysis is another anatomic etiology of aspiration. This condition places patients at risk for aspiration by means of both decreased sensation and a limitation of the typical airway protective mechanisms. It can be diagnosed

with a bedside flexible scope in an awake patient. Tabaee et al. showed that in a bedside flexible endoscopic exam of 81 patients with unilateral vocal cord paralysis, 23 % had frank aspiration, 25 % had penetration, and 56 % had pooling [35]. Risk factors for vocal cord paralysis include cardiothoracic surgery, prolonged intubation, and neurologic conditions, among others. Reports have shown that up to 20 % of patients suffer from vocal cord paralysis after esophageal atresia repairs [36]. After cardiothoracic surgery, up to 10 % of patients have abnormal swallowing and of these patients, only 35 % of patients recover vocal cord function without surgery [37]. The natural history of this disorder involves significant morbidity and the median time to resolution of vocal cord paralysis is varied, ranging from 2.3 months for neurologic causes to 5.9 months for idiopathic with a wide range for all causes from 0.4 to 38.7 months [38]. Again, understanding the natural history is critical; if vocal cord function is expected to improve, then the goal of management is to avoid a permanent feeding tube and either feed with thickened feeds or an NG tube.

Other Conditions

There are a number of other conditions that can also cause swallowing dysfunction. These include enlarged tonsils, tongue-tie, macroglossia, and sub-mucosal cleft palate in addition to other congenital anatomic abnormalities such as tracheoesophageal fistula and oropharyngeal facial anomaly syndromes such as CHARGE syndrome and Pierre-Robin sequence. Any disorders of motility or esophageal inflammation can cause dysphagia, impact swallowing, and cause dysfunctional eating including food restriction, pocketing of food, and gagging, among others, but other chapters will address this concern. Many of these will be discussed in other chapters.

Upper esophageal dysfunction is another condition that can place infants at risk for aspiration. This dysfunction can range from a complete lack of relaxation to dyscoordination of pharyngeal contraction and UES relaxation. Studies in neonates with hypoxic-ischemic encephalopathy had higher rates of abnormal pharyngeal-upper esophageal sphincter dyscoordination and increases UES basal tone [39]. Premature infants and those under 34 weeks in particular often suffer from low and therefore poor pharyngeal pressures at the laryngeal inlet combined with incomplete coordination of upper esophageal sphincter relaxation. This combination of defects makes appropriate swallowing difficult and more likely to result in laryngeal pooling and choking episodes [40]. In infants with acute life-threatening events, there are also subtle UES abnormalities compared to healthy infants; there is a faster post-deglutitive rise in UES pressures which may impact the effectiveness of bolus clearance from the pharynx though studies with impedance and manometry (to assess bolus movement) are needed to prove if this is clinically significant [41]. There are conflicting results about the impact of gastroesophageal reflux on the upper sphincter; some studies show no effect while others show a lower resting upper esophageal sphincter pressure, which might allow for easier passage of full column refluxate into the larynx and the airway [42, 43].

The treatment for UES dysfunction includes Botulinum toxin injection to the UES or dilation. While there are only isolated case reports in pediatrics, a review of the adult literature supports benefit to both. For example, in adults with aspiration, injection of Botox into the UES of patients with dyscoordination resulted in transition to full oral feeding in 70 % of patients who were initially tube fed [44]. In another adult study, 65 % of patients had improvement in dysphagia symptoms though there can be transient worsening in the immediate postoperative period [45]. In a small blinded radiologic study, there was significant improvement in bolus movement and the presence of residue in 6/8 patients who received cricopharyngeal Botox [46]. Interesting, even one injection may have long-lasting benefit on the function of the UES [47]. Again, while there are no pediatric studies, balloon dilation of patients with UES dysfunction has beneficial results with up to 80 % of patients resuming oral feeding after dilation [48]. As with any therapy, the risks need to be weighed against the benefit and the risks can include with Botox and/or dilation, perforation, paralysis of the vocal cords, and worsening of aspiration and gastroesophageal reflux due to a loss of the UES protective barrier.

Finally, aspiration can be caused by abnormalities in the suck-swallow-breathe cycle that is a result of a primary respiratory problem or secondary to other medical issues such as underlying cardiac disease. This is seen in children with laryngomalacia as a result of respiratory distress leading to poor swallow coordination [2]. Likewise, studies have suggested that infants with bronchiolitis can also have transient swallow dysfunction, which resolves over time as they overcome the infection and resultant pulmonary inflammation [49]. Finally, in patients with acute changes in respiratory status such as after supraglottoplasty, there can be a worsening of aspiration and swallowing function though this degree varies depending on the institution [50–53]. These situations suggest that there are a variety of conditions that when overlaid on normal swallowing can cause clinically significant dysfunction, which likely needs to be addressed until the insult resolves.

Management of Swallowing Dysfunction

There are a number of considerations for the management of swallowing disorders in pediatrics. Swallowing dysfunction and aspiration therapies are guided by the diagnostic test, the

severity of dysfunction, the complications from this dysfunction, and the expected natural history of the underlying cause for this dysfunction. Aspiration treatment options include thickening of feeds, feeding therapy, gastrostomy and gastrojejunostomy tubes, fundoplication, and pharmacologic approaches. Anatomic abnormalities that lead to aspiration can often be addressed surgically with the help of general and otolaryngology surgeons. The management of patients with normal upper airway anatomy can be more challenging, however, and we typically recommend feeding and swallowing therapy for these children [27].

Oropharyngeal dysphagia with aspiration can be treated with thickening of feeds without the need for gastric tubes in the majority of cases and this continued oral feeding with thickened liquids has superior outcomes than feeding with enteral tubes [28]. Most pediatric patients will be able to tolerate some degree of thickening and the videofluoroscopic study can guide which textures are safe to eat and which improve the quality of swallowing. Thickening has been shown to improve swallow function by slowing down the velocity at which the bolus travels through the oral and pharyngeal phases of swallowing, increase the duration of pharyngeal contractions and prolong and increase opening of the upper esophageal sphincter [54]. Rofes et al. showed that increasing bolus viscosity using a commercial xanthan gum thickener improved the safety of swallowing by decreasing aspiration and penetration events on swallow studies [55]. This thickening continues until the swallowing dysfunction resolves as the infants mature or until the child's clinical situation improves [26]. It is also important to note that several studies have failed to show any evidence of dehydration from thickening feeds, so the worry that children will dehydrate on honey thick or even purees is not substantiated [56]. Another important aside is that thickening will also treat gastroesophageal reflux disease and decrease spit-ups and therefore weaning of thickening may result in worsening reflux which may appear as if aspiration is worsening again [57].

For patients who aspirate all consistencies, enteral tubes are frequently utilized to enable safe enteral feeding. Nasogastric tubes are frequently the first approach but if the condition does not improve these children frequently require gastrostomy tubes. Gastrostomy or gastrojejunostomy tubes require surgical placement but are sometimes the only option for these children. Although both enteral tube options enable a bypassing of the upper airway, feeding into the stomach can sometimes lead to aspiration reflux gastric contents. Metheny et al. showed that placing feeding tubes in the postpyloric position such as the duodenum or the jejunum does significantly reduce the risk of aspiration, especially in critically ill hospitalized children [58]. There are no studies to compare the rates of pulmonary complications in patients that are fed into the stomach or postpylorically in patients with isolated swallowing dysfunction.

Because many causes of swallowing dysfunction improve over time, the goal of therapy is to "buy time" until the swallowing function improves, whether by thickening or by nasogastric tube placement. Evidence supports this approach to avoid permanent feeding tubes. We have previously shown in a comorbidity matched case control study that children who undergo gastrostomy tube placement higher morbidity and hospitalization rates related to the tube presence with no increase in pulmonary complications suggesting that whenever possible, oral feeding should be continued [28, 59]. In addition, early NPO status and prolonged NPO duration have been shown to lead to worse swallowing decline in the long term, so even in patients with aspiration of all textures, many centers allow a small amount of continued oral feeding to preserve the feeding skills [60]. Finally, there are ethical considerations that must be weighed when making decisions about feeding and swallowing, particularly in cases of severely neurologically impaired children whose families want to continue oral feeding for quality of life or in families who are making end-of-life decisions [61].

Fundoplication is an additional surgical option sometimes pursued for patients with intractable aspiration with the idea that if patients are aspirating during swallowing, they are at greater risk of aspirating gastroesophageal reflux. Despite this concern, multiple studies have failed to show a consistent benefit to fundoplication for the treatment of aspiration pneumonias [62]. In some cases, aspiration can even worsen after fundoplication due to pooling of saliva and food above the fundoplication. In addition, fundoplication can lead to additional adverse effects such as retching and other forms of feeding intolerance and as a result these procedures have fallen out of favor at many pediatric centers [63–65].

Medications are also sometimes utilized in children who aspirate. Many providers will place patients on acid suppressing medications, such as proton pump inhibitors, based on the theoretical premise that acidic irritation of the pharyngeal structures might cause desensitization that leads to a decrease in the airway protective mechanisms that prevent aspiration. Despite this, proton pump inhibitors have not been shown to reduce the rates of aspiration pneumonias [66]. In addition to the unclear efficacy of acid-blocking agents in patients with aspiration, use of these medications has very clearly been associated with significant risks, including increased risk of both gastrointestinal and pulmonary infections in the pediatric population [67]. Additionally, changes in the enteric microbiome brought about by these medications can negatively impact the lungs [67–70].

Other groups have attempted to use pro-motility medications such as erythromycin and azithromycin. These medications can both decrease proximal reflux and increase gastric emptying, which might decrease the occurrence of gastric aspiration [71, 72]. They do not, however, seem to have any effect on the occurrence of oropharyngeal aspiration.

Treatment of swallow dysfunction requires experts skilled in the evaluation and management of the myriad causes of aspiration. The evaluation and care for these children must therefore take place in a multidisciplinary setting in order to best serve their needs. The team should include various members including gastroenterologists, speech language pathologists, pulmonologists, and otolaryngologists and also requires thoughtful collaboration with radiology and nutrition specialists. Multidisciplinary management of these patients not only leads to better outcomes, it is also more cost-effective and results in greater patient and family satisfaction [73].

Conclusion

The diagnosis and possibly the incidence of swallowing disorders is increasing and so it is important to make these diagnoses earlier to prevent both the dangerous effects of untreated aspiration and in the cases of developmental dysphagia to start interventions earlier to best increase chances of success. A multidisciplinary team is essential for a coordinated and effective evaluation and management strategy for pediatric patients with oropharyngeal dysphagia. Varied causes have been discussed but with appropriate therapies the prognosis for swallowing disorders remains optimistic.

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Esophageal Achalasia

21

Ann Aspirot

Achalasia is the most recognized esophageal primary motor disorder presenting with dysphagia secondary to functional obstruction due to the affection of the body of the esophagus and the lower esophageal sphincter. It is characterized by the absence of peristalsis and incomplete relaxation of the lower esophageal sphincter.

Epidemiology and Incidence

Achalasia is an infrequent adult disease with an incidence of 1.63/100,000 and a prevalence of 10.82/100,000, according to a Canadian population-based study [1]. Mean age at diagnosis was 53.1 years, and the survival is less than age-matched healthy control. Because of the relative rarity of childhood and adolescent achalasia, much of the literature on achalasia is based on the adult population with limited high-quality evidence on the pediatric aspects. The incidence of achalasia before 16 years is much lower but is rising. An incidence of less than 0.1/100,000 per year has been found in children in England and Wales in 1988 [2], compared to at least 0.18/100,000 per year in a study published in 2011 [3]. A mean incidence of 0.1/100,000 per year was also found in the Netherlands [4]. In contrast to the adults, pediatric achalasia seems to be slightly more frequent in boys than in girls, and most of the cases are diagnosed between 7 and 15 years. Infants are rarely affected (6 %), but symptoms are described to be present during the first year of life in 18 % [5]. Infantile achalasia is reported as case reports in the literature [6]. Diagnosis may not be as rigorous in young children as it is in adults [2], many published cases were not confirmed by esophageal manometry, the gold standard diagnostic tool. In a recent study, 38 % of the patients did not have manometry secondary to inability to tolerate the procedure [7].

Pathophysiology

Acquired degeneration of the Auerbach's myenteric plexus is the primary mechanism of achalasia. Loss of nitrergic inhibitory enteric neurons occurring prior to loss of cholinergic neurons results in an imbalance between excitatory and inhibitory input leading to ineffective esophageal peristalsis and incomplete lower esophageal sphincter relaxation [8, 9]. Nitric oxide (NO) is the predominant inhibitory neurotransmitter, but others have been described such as vasoactive intestinal peptide (VIP). Studies on resected specimen have demonstrated decreased number of myenteric ganglia, lymphocytic infiltrate, and collagen deposition within ganglia. Some specimen had normal number of myenteric ganglion cells, but myenteric fibrosis was observed. Preservation of cholinergic excitatory neurons could explain the occurrence of vigorous achalasia which has been hypothesized to be an earlier form of the disease [10]. These findings suggest a progressive immune-mediated destruction of neuronal cells. The pathologic findings could be different in childhood achalasia where less neuronal inflammation was found [11]. A decrease or absence of NO synthase-containing nerve fibers has also been described in children with achalasia [12].

Etiology

Achalasia can be primary (idiopathic) or secondary. Chagas disease is the prototype of secondary achalasia that is caused by the flagellate protozoan *Trypanosoma cruzi*. The disease is common in South and Central America, but a decline in the number of younger patients has been observed, most likely because of better sanitary measures aimed at controlling the transmission of the parasite [13]. Whether the disease is

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similar to idiopathic achalasia remains controversial [14]. In Chagas megaesophagus, there is not only denervation of inhibitory neurons but also of excitatory cholinergic neurons. These differences do not seem to have therapeutic implication. Pseudoachalasia is also a secondary form of achalasia. Possible causes include primary malignancy of the esophagus or esophagogastric junction, secondary malignancies such as metastases from the lung and breast, benign tumors, amyloidosis, central or peripheral neurological disorders, postoperative complication after an antireflux surgery, and paraneoplastic syndromes in the context of small-cell carcinoma, bronchial carcinoid, gastric carcinoma, and pleural mesothelioma [15].

The etiology of primary achalasia remains unknown. Numerous hypotheses have been proposed including infection, autoimmunity, and hereditary. All three hypotheses may be linked together [16]. Chagas disease is the proof that achalasia can be caused by infective agents. In idiopathic achalasia, viruses have been suspected because of the associated inflammatory infiltration mainly composed of lymphocytes. Herpes simplex virus 1 (HSV-1), varicella-zoster virus, measles, and human papillomavirus have been proposed. The presence of such viruses in esophageal samples has been difficult to demonstrate [17, 18], possibly because the reservoir of the virus, the myenteric ganglia, is destroyed. HSV-1-reactive lymphocytes have been identified in lower esophageal sphincter muscles of achalasia patients [18, 19]. Recently, HSV-1 DNA, RNA, and virus were detected in the lower esophageal sphincter biopsies from achalasia patients [20]. A cause–effect relationship between viruses and achalasia has yet to be identified, but these infective agents could trigger an autoimmune-mediated ganglionitis [10, 20, 21]. There is evidence that achalasia has an important local and systemic inflammatory autoimmune component with the presence of anti-myenteric autoantibodies [20]. The significance of the antineuronal antibodies has been questioned [8, 22], but in another study, the serum of achalasia patients reproduced the phenotype and functional changes that occur with achalasia in an ex vivo human model [23]. Since not all the infected patients develop the autoimmune cascade leading to achalasia, a genetic predisposition is strongly suspected. Achalasia has been associated with specific HLA class II molecules [24, 25]. The genetic link is also suggested by studies reporting association between achalasia and trisomy [21, 26, 27], Hirschsprung's disease [28], Allgrove's syndrome [29–34], Rozycki syndrome (deafness, short stature, vitiligo, muscle wasting, and achalasia) [35], Alport syndrome [36], growth hormone deficiency [37], and autism [38]. However, familial history is the exception in achalasic patients even in the pediatric age [5, 39]. Few case reports of monozygotic twins without multisystem disorders have been published [40, 41]. Most of the familial occurrences described in the literature are due to Allgrove (also called 4 "A" or triple A) syndrome, which is worth mentioning because it is the only condition associated with achalasia that has been linked to a specific chromosomal anomaly which is the AAAS or ALADIN gene on chromosome 12q13 [30–32]. Allgrove syndrome is an autosomal recessive condition characterized by achalasia, alacrima, autonomic disturbance, and corticotrophin (ACTH) insensitivity. In adults, progressive neurological disease has been described. It usually presents during the first decade of life with dysphagia, hypoglycemic, or hypotensive attacks. A histopathologic study revealed fibrosis of the intermuscular plane and a lack of neuronal NO synthase, explaining the defective cardiac relaxation [32]. Because of the rarity of achalasia in childhood and the fact that most cases of Allgrove syndrome have no family history, it is important to refer younger patients with suspected achalasia to Genetics and screen for adrenal insufficiency to assess the possibility of Allgrove syndrome. Patients with Allgrove syndrome seem to present a more severe course than patients with idiopathic achalasia despite early diagnosis with family screening. Higher LES pressure has also been noted in some patients with this syndrome [42].

Clinical Presentation

Achalasia presents with progressive dysphagia (first for liquids and eventually for solid food), chest pain, and regurgitation of undigested food, not mixed with gastric secretions [43]. Nurko and Rosen [44] summarized the clinical symptoms in 528 pediatric patients from 23 series. The most common symptoms are vomiting (80 %) and dysphagia (75 %). Weight loss is reported in 64 % and failure to thrive in 31 %. Chest pain and odynophagia is sometimes present (45 %), but less common in younger children. Diagnosis is often delayed in young children because of multiple factors including lower incidence of achalasia, incapacity to verbalize complaints, and unspecific symptoms, such as food refusal and failure to thrive. Parents will sometimes report that their child is a slow eater. Children additionally present nocturnal symptoms such as choking and regurgitated food on the pillow (21 %). Respiratory symptoms occur in 44 % which is more frequent than in the adult population. In young children, regurgitation, respiratory problems, and failure to thrive are easily attributed to gastroesophageal reflux (GER) which is much more predominant than achalasia in this population. Extraesophageal complications of achalasia include recurrent pulmonary aspirations and tracheal compression by the megaesophagus. Sudden death has also been reported.

Differential Diagnosis

Achalasia symptoms are similar to more prevalent problems in childhood such as GER, feeding aversion, asthma, and eosinophilic esophagitis [45]. Differential diagnosis include mechanical obstruction by foreign body, intrinsic esophageal pathology (esophageal stenosis, leiomyomas), and extrinsic compression of the esophagus (foregut duplication, mediastinal tuberculosis). Malignant neoplasms are more frequently seen in the adult population but need to be included in the differential diagnosis even in children. Megaesophagus has been described in a case of H-type tracheoesophageal fistula [46]. Chagas disease is always a possibility in patients coming from endemic regions. Achalasia has also been mistaken as eating disorders [47, 48], emphasizing the importance of a thorough evaluation of the upper gastrointestinal tract anatomy and function in patients suspected of having primary anorexia nervosa.

Diagnosis

Diagnosis is first suspected by the history but is often delayed because of the nonspecificity of the symptoms and the confusion with other more frequent pathologies such as GER disease. The specific work-up includes radiographic studies, upper endoscopy, and esophageal manometry to confirm the diagnosis of achalasia.

Radiography

Plain chest radiograph may show an air-fluid level in the lower chest, a widened mediastinum, and an absent gastric bubble [49]. Contrast esophagogram will demonstrate the stagnation of contrast in the distal esophagus and possibly absent or tertiary peristalsis. The typical dilated esophagus tapering smoothly at its distal end ("bird's beak") is not necessary to make the diagnosis, but is highly suggestive of the disease. Using manometry as the gold standard, Parkman found a positive predictive value of 96 %, a sensitivity of 100 %, and a specificity of 98 % [50]. However, the correlation of severity as assessed by esophagogram and patient's symptoms is poor, which can also lead to a delayed diagnosis [51]. Timed barium swallow has been described to assess esophageal emptying [52, 53]. This test can also be useful to monitor the success of treatment.

Endoscopy

Upper endoscopy may show retained food in a dilated esophagus. The gastroesophageal junction may appear tight (difficult to distend with air insufflation), but it is usually possible to reach the stomach. The main goal of upper endoscopy is to rule out mechanical obstruction at the gastroesophageal junction (pseudoachalasia) [54]. If pseudoachalasia is suspected, further investigation with ultrasound, endoscopic ultrasonography, and other imaging studies will help to differentiate between the numerous neoplastic and nonneoplastic causes of pseudoachalasia [55].

Manometry

The diagnosis of achalasia is confirmed by esophageal manometry. Absence of peristalsis in the esophageal body is the sine qua non criteria to diagnose esophageal achalasia [43]. Frequently, the lower esophageal sphincter relaxation is incomplete [56, 57]. Hypertensive lower esophageal sphincter is sometimes seen as well as an increased esophagogastric gradient. Recently, high-resolution manometry (HRM) has permitted a better understanding of the motility abnormalities found in achalasia and a classification in three subtypes [58]. HRM imaged with color pressure topography plots has become the gold standard for categorizing the esophageal motility disorders (Figs. 21.1, 21.2, and 21.3). In the latest version (v3.0) of the Chicago Classification (CC) published in 2014, achalasia is included in the disorders of esophagogastric junction (EGJ) [59]. Pressure topography metrics that are necessary to characterize achalasia are the median integrated relaxation pressure (IRP), the distal contractile integral (DCI), and the intrabolus pressure pattern (30 mmHg isobaric contour referenced to atmospheric). The criteria are:

- Type I achalasia (classic achalasia): Elevated median IRP (more than 15 mmHg), 100 % failed peristalsis (DCI less than 100 mmHg s cm).
- Type II achalasia (with esophageal compression): Elevated median IRP (more than 15 mmHg), 100 % failed peristalsis, panesophageal pressurization of more than 30 mmHg with at least 20 % of swallows.
- Type III achalasia (spastic achalasia): Elevated median IRP (more than 15 mmHg), no normal peristalsis, premature (spastic) contractions with DCI more than 450 mmHg s cm with at least 20 % of swallows.
- EGJ outflow obstruction: Elevated median IRP (more than 15 mmHg), sufficient evidence of peristalsis such that criteria for types I–III achalasia are not met.

The prevalence of the different subtypes is quite variable between the studies (type I, 11–47 %; type II, 32–52 %; type III, 6–57 %) [58, 60, 61]. EGJ outflow could be an incompletely expressed achalasia or an early achalasia. In adults, it should be further investigated by endoscopic ultrasound to rule out a subtle infiltrative disease or cancer [62]. It is sometimes complex to measure relaxation of the lower esophageal sphincter in cases of absent contractility. In these cases, bolus retention on a barium esophagogram will suggest achalasia [63].

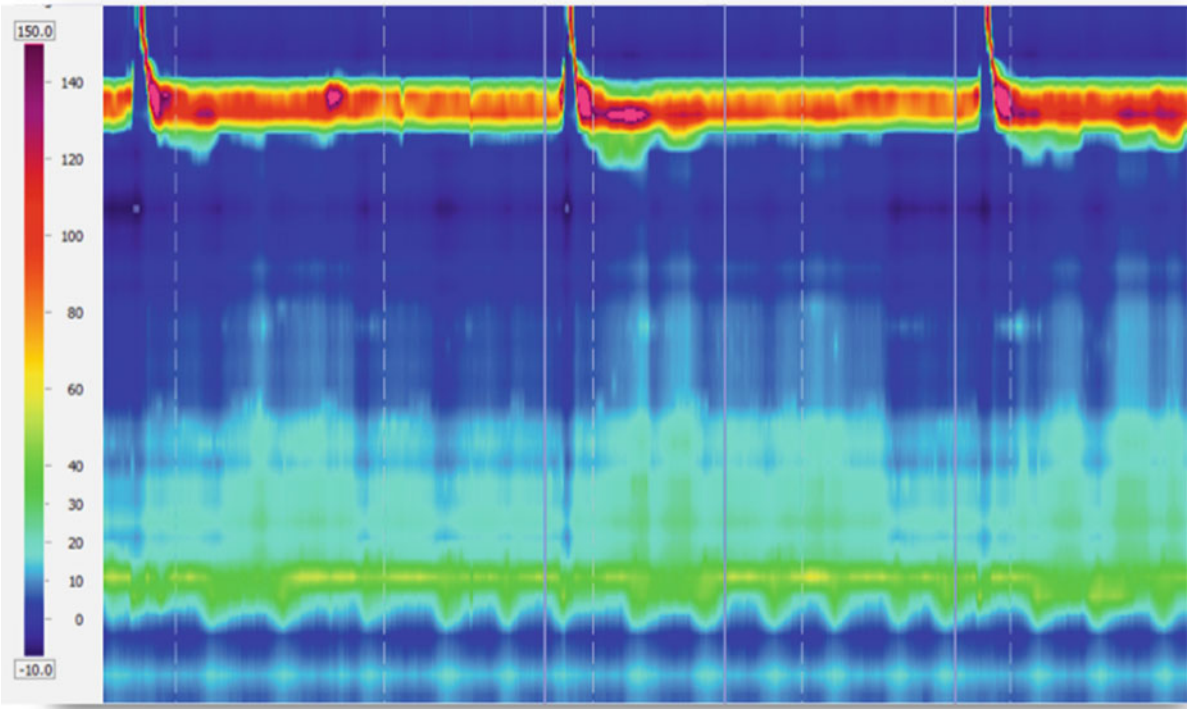

Fig. 21.1 Type I esophageal achalasia (IRP 33 mmHg)

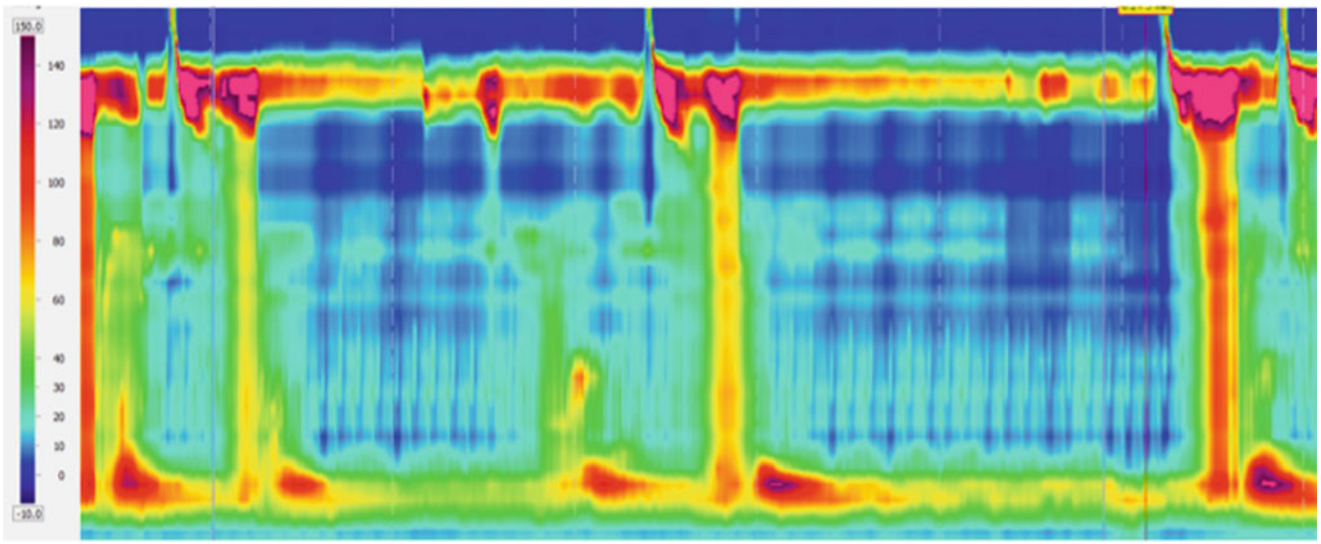

Fig. 21.2 Type II esophageal achalasia (IRP 43 mmHg)

In children, HRM is easier to perform than conventional manometry and is also required to establish the diagnostic. The same subtypes are seen in children (39 % of type I, 50 % of type II, 11 % of type III). Different responses to the administration of multiple liquid swallows are seen depending of the subtypes [64]. According to Morera et al. [65], LES function in children is heterogeneous (different responses in swallows). In their cohort of 29 patients with achalasia, partial relaxations were common, and normal relaxations were possibly present. These findings suggest a different physiopathology in pediatric achalasia.

Treatment

Treatments for achalasia, similar to other esophageal disorders, focus on relieving symptoms [66], and there is no curative therapy. Apart from relieving symptoms, the goals of treatment are to improve esophageal emptying and to prevent the development of megaesophagus [67]. The three primary types of treatment are pharmacologic, endoscopic, and surgical. They all are directed at improving esophageal emptying by decreasing the LES pressure. The therapy of choice in children is still

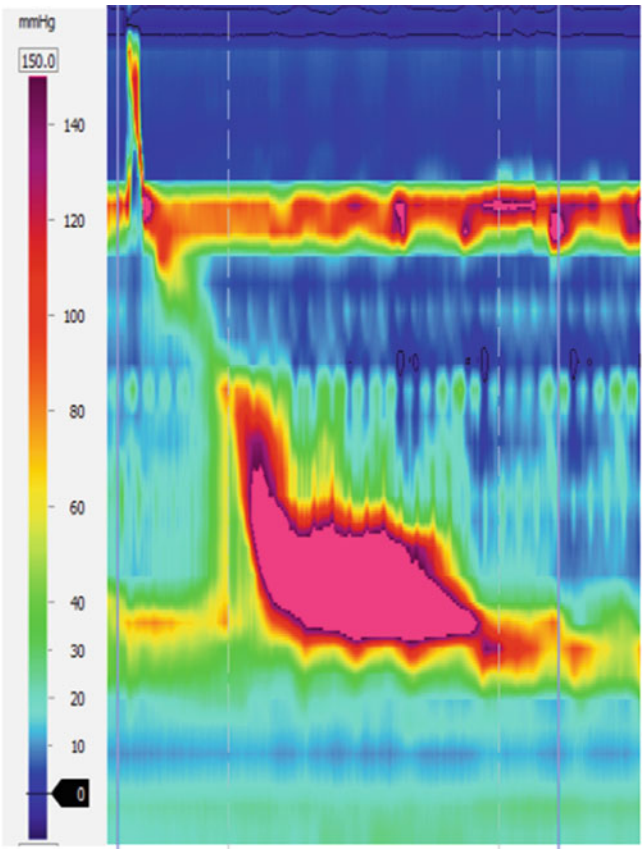

Fig. 21.3 Type III esophageal achalasia (IRP 55 mmHg, distal latency 3.9 s)

debated [68]. Proper treatment of achalasia is important to prevent progression toward dilated megaesophagus where esophagectomy may become inevitable. Barium esophagogram can help monitor success of the treatment plan.

Pharmacologic treatments include nitrates, calcium channel blockers, and phosphodiesterase inhibitors. Although significant decrease of lower esophageal sphincter pressure has been observed by manometry, symptom improvement occurred in 53–87 % of patients [69]. In some cases, these medications are used temporarily while determining a more effective means of treatment. Pharmacologic interventions are also the treatment of choice for patients who are not candidates for or do not wish to receive more aggressive therapy. These medications have frequent side effects (headache, hypotension). Experience in children is limited to calcium channel blockers and nitrates and consists mainly of case reports [70–72]. Isosorbide dinitrate patch (long acting nitrate) has been reported in an 8-year-old [71] with good short-term success. Nifedipine (10 mg) before meal was used in four adolescents with good clinical response and a decrease of LES pressure on manometry, but there was recurrence of symptoms when the medication was stopped [70]. Long-term pharmacologic therapy is not actually recommended. Short use can be useful while waiting for definitive therapy (establishing weight gain, awaiting school vacation).

Endoscopic therapies include botulinum toxin injection (BTI) into the LES, pneumatic dilation (PD), stenting, and the newest per oral endoscopic myotomy (POEM). The use of intrasphincteric botulinum toxin was first reported by Pasricha et al. [73]. This potent neurotoxin blocks the release of acetylcholine at the neuromuscular junction leading to decreased LES pressure. A double-blind placebo-controlled trial demonstrated a good initial response in adults [74]. BTI is widely used as an initial endoscopic therapy in achalasia in older adults [75]. Long-term results show that it is necessary to repeat injection and the response decreases with repeated injections [76]. Experience in children is once again limited to retrospective case series [77–80], but shows similar results of good initial clinical response and high rate of recurrence. The data are however insufficient to conclude to the same certitude as in the adult population. BTI can also be used as a diagnostic tool in patients with early and unclear diagnosis [81]. However, submucosal fibrosis resulting from intrasphincteric injections may complicate the subsequent surgical myotomy [82].

Esophageal dilation is the oldest treatment modality [43]. Balloon PD is preferred over rigid bougienage because it is thought to permit a controlled tearing of the muscle fibers, even though it was not proven in animal studies [83]. It is less invasive than surgical treatment and is considered the most effective nonsurgical treatment of achalasia in adults [84, 85] and the first-line treatment in some pediatric centers [68]. A Cochrane review concluded that PD was more effective than BTI in the long term [86]. The main complication is esophageal perforation which was reported in 1.6 % of patients [84, 85]. Long-term efficacy of PD ranges from 40 to 60 % [87–89]. Pediatric results are variable and difficult to compare because of the nonstandardization of the technique [44]. PD can also serve as a rescue therapy after an incomplete myotomy [49].

Temporary self-expanding metallic stent is a therapeutic option that has been described but is rarely used. Use in patients as young as 12 years old has been described, but more studies and long-term experience is needed before recommending it [90].

With the advent of natural orifice transluminal endoscopic surgery in 2004, new techniques were developed in the animal laboratory to perform typical laparoscopic procedures by endoscopy through natural orifice. A primary focus of research in that field was to ensure secure closure of the transluminal access track that is used to enter the mediastinum or peritoneal cavity [91]. The first human endoscopic LES myotomy for achalasia was performed by Inoue in 2008, in Yokohama, Japan. He called it POEM in his presentation at Digestive Disease Week 2009 [92]. The technique consists of a flexible endoscopy with CO_2 insufflation to perform an esophageal mucosotomy followed by a submucosal tunnel all the way to the gastric cardia to realize a longitudinal incision in the inner circular muscle. The mucosotomy is

closed with multiple endoscopic clips. The technique requires general anesthesia, advanced endoscopic expertise, and availability of surgical back up. Since the first reported experience, multiple centers started to use this technique worldwide, and the experience is growing exponentially. The technique appears to be a safe and effective treatment for achalasia. Reported adverse events were caused by infection, bleeding, or gas diffusion in the thorax, abdomen, or subcutaneous tissue [93]. Use of carbon dioxide has decreased the incidence of the gas complications, but decompressive aspiration with a needle is often required [94]. Even with the absence of hiatal attachments, dissection, and disruption of the angle of His, posttreatment gastroesophageal reflux is frequent (15–29 %) [95]. With the limited follow-up of this newly described technique, accumulating data suggest POEM efficacy at least similar to that of LHM [95, 96] even on the long term, with 88.5 % overall success rate at 3 years [97]. The longer myotomy length with POEM could improve the rate of success to greater than 90 % in patients with type III achalasia [98]. POEM is also feasible in children. Several case series of successful POEM have been reported in the pediatric population [99–101]. The largest pediatric series of 27 children aged between 6 and 17 years old reported feasibility of 96.3 % and treatment success in all cases with a mean follow-up of 25.6 months (range 15–48 months) [102].

Surgical treatment usually consists of a longitudinal division of the muscle fibers of the LES and proximal stomach coupled or not with antireflux procedure. The name of Heller myotomy comes from the first description of this procedure by Ernest Heller in 1913 [66]. Laparoscopic Heller myotomy (LHM) is now the most commonly performed surgical treatment of achalasia because it reduces the morbidity compared to the open approach. It has been shown to be as effective as open approaches [103] and superior to the thoracoscopic approach [104, 105]. Clinical response after myotomy ranges from 83 to 100 % [106], and the benefits persist in 67–85 % in long-term (more than 10 years) studies [107, 108]. A meta-analysis concluded that LHM was the most effective surgical technique. It provides better symptom relief than all endoscopic and other surgical approaches with a low complication rate (6.3 %) [84]. Randomized controlled trials compared favorably LHM to PD [109–112]. It has been suggested that a more aggressive balloon dilatation results in comparable results to myotomy [113, 114]. A large multicentric randomized control trial in Europe comparing PD versus LHM with Dor's fundoplication found no differences in terms of success rate, posttreatment LES pressure, esophageal emptying, or quality of life [115]. Clinical deterioration over time has been associated with GER [116] which has led to randomized controlled studies comparing Heller myotomy with and without fundoplication [117]. The different types of fundoplication have also been discussed and compared in randomized clinical trials [118, 119]. Based on long-term success rates of 47–82 % at 10 years, LHM with partial fundoplication is considered by many the surgical procedure of choice [84, 120, 121]. However, a study has reported that up to 30 % of myotomized patients will require retreatment within the first 12 years [122].

LHM has also been found safe and effective in children [123, 124]. Rates of good to excellent results of 90.9 % have been reported [125–127]. However, pediatric studies comparing LHM to PD show conflicting results [49, 68, 128–133]. As in the adult literature [134], the same surgical controversies exist which include extension of the myotomy [135, 136], addition of fundoplication [137], and type of fundoplication if performed. Complications after LHM include esophageal perforation, phrenic nerve paralysis, hemorrhage, and herniation of stomach. Long-term complications are persistent dysphagia and GER. The intraoperative use of endoscopy [138], esophageal manometry [139], and dilation under image guidance [140] has been suggested to decrease the rate of incomplete myotomy. It is important to emphasize that while myotomy should improve the bolus transit by reducing the LES pressure, ineffective peristalsis still remain an issue [141].

An approach to the child with persistent dysphagia after myotomy has been proposed since it is a frequent and debilitating problem [142]. Differential diagnosis of this problem include esophageal dysmotility, incomplete myotomy, fibrosis at the distal end of the myotomy, obstructive fundoplication, esophageal stricture, and preoperative misdiagnosis [143–145]. A thorough evaluation is the basis of management, starting with a good clinical history. Contrast esophagogram and esophageal manometry complete the initial work-up. Depending of the findings, endoscopy with PD may be indicated as the first therapeutic step. Surgical treatment is reserved for persistent significant obstruction of the distal esophagus [142].

Outcome

The different subtypes of achalasia seem to have a prognostic value [60, 146]. Patients with type II have the best response (96 %) to PD or LHM; patients with type I have 81 % success, but this decreases as the pretreatment esophageal dilatation increases; patients with type III have the worst response (66 %) [146]. Others have questioned the clinical implication of the subtypes both based on clinical relief of symptoms and on improvement in esophageal clearance [147]. In children, correlation between the subtypes and the outcome is also not clear [64].

Different validated scoring systems have been developed to evaluate the treatment response. One of the mostly used is the Eckardt clinical score [148] which is the sum of symptom scores for dysphagia, regurgitation, chest pain, and weight loss

Table 21.1 Eckardt clinical score for evaluation symptom severity for achalasia (total maximum score is 12)

Symptom	Each meal	Daily	Weekly	None
Dysphagia	3	2	1	0
Regurgitation	3	2	1	0
Chest pain	3	2	1	0
Weight loss	More than 10 kg	5–10 kg	Less than 5 kg	No weight loss
Score	3	3	1	0

From Greene CL, et al. High resolution manometry subclassification of Achalasia: does it really matter? Does Achalasia subclassification matter? Surg Endosc 2015;29(6):1363–7, with permission

(Table 21.1). Physiologic tests are the best predictors of long-term success of treatment [16]. A manometry can be used to assess the success if tolerated. A study noted that 66% of patients with post-procedure LES pressure less than 15 mmHg were in symptomatic remission after 6 years [149]. Older anecdotal reports of return of peristalsis have recently been confirmed by HRM [150]. Timed barium esophagogram is a better predictor of success than is LES pressure [151]. More recently, EndoFLIP system (Crospon, Galway, Ireland) has been used to measure the distensibility of the EG junction with a balloon catheter passed across the LOS during an endoscopy. This parameter seems better than LES pressure for evaluating efficacy of treatment for achalasia [152].

Regardless of the elected therapy, patients must continue with regular follow-up. Periodic evaluation of symptoms, nutrition status, and growth is essential, especially in children and adolescents. Timed barium esophagram seems to be superior to manometry and easier to tolerate. Endoscopic surveillance is not indicated in children, but might be beneficial after a disease duration of more than 10–15 years [153] because of the rare, yet possible development of squamous cell carcinoma in the esophagus. It is thought to result from stasis and uncontrolled bacterial growth [154]. Based on a review of the literature, Dunaway has reported a mean prevalence of 3% which represents of 50-fold increased risk over the general population [155]. Chronic gastroesophageal reflux resulting from the successful treatment of achalasia is also a risk factor for the development of adenocarcinoma [156, 157]. More recently, a prospective cohort study of 448 achalasia patients reported esophageal cancer in 3.3% with an annual incidence of 0.34 and, despite structured endoscopic surveillance, most neoplastic lesions were detected at an advanced stage [158]. Up to now, no cases of esophageal carcinoma have been reported in patients who had achalasia diagnosed as children [44]. The overall life expectancy of patients with achalasia does not appear to be significantly decreased [159], but the quality of life in adulthood is decreased [4, 160]. Some have found that children with achalasia have a significantly lower quality of life compared to children with inflammatory bowel disease and healthy children [161]. Others did not find a difference [4].

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Other Esophageal Motility Disorders

22

Hayat Mousa

Diffuse Esophageal Spasm and Nutcracker Esophagus

Diffuse esophageal spasm (DES) and nutcracker esophagus (NE), also known as hypertensive peristalsis, are benign and very rare, representing less than 10 % of abnormal adult manometry tracings [1–3]. The incidence in children is not known and the literature is scarce, limited to case reports and small case series [4, 5]. In a retrospective study of 278 children who underwent esophageal manometry, 36 patients (13 %) had DES, with the most common complaint among children under 5 years old being food refusal [6].

With the development of high-resolution manometry (HRM) and specific metrics to characterize esophageal motility, the Chicago Classification has become the gold standard for the diagnosis of esophageal motor disorders in adults [7, 8]. It still requires adjustments to apply to the pediatric population [9]. Initially using conventional manometry, DES was diagnosed when there were simultaneous esophageal contractions in more than 20 % of liquid swallows, with other swallows showing normal peristalsis. These were always nonspecific findings, but HRM and esophageal pressure topography (EPT) have led to a more robust definition. Premature contractions with normal EGJ relaxation are more specific for DES. On HRM, nutcracker esophagus is characterized by prolonged, hypertensive contractions in the context of normal propagation of the swallow waveform and normal lower esophageal sphincter relaxation [8, 10]. HRM also shows a distal contractile integral (DCI) of over 5000 mmHg.s.cm. By standard manometric definition, average distal esophageal peristaltic pressures measure over 220 mmHg in at least 30 % of swallows [11]. Barium esophagograms are often normal in DES and NE patients [12], but do show typical corkscrew appearance in a minority of DES patients.

Both DES and NE share symptoms of intermittent dysphagia and chest pain, with or without swallowing [1, 12–14]. Symptoms are usually experienced while eating or drinking [1, 12]. DES tends to present comorbidly in infants and children [6]. Infants may additionally present with apnea and brachycardia and younger children with aspiration pneumonia; symptoms of older children most resemble those observed in adults [15]. Because symptoms are intermittent, it is easy to distinguish these two conditions from more progressive diseases (i.e., achalasia and esophageal cancer) [12].

The etiology and pathogenesis of both conditions remain unknown [1], and due to insufficient understanding of the pathogenesis, treatment remains difficult. Several reports have described patients with DES, nonspecific esophageal motor disorder (NSEMD), nutcracker esophagus, and gastroesophageal reflux disease (GERD) progressing to achalasia [16–18]. Although no causal relationship has been identified, these reports suggest that the different esophageal motor disorders represent a spectrum rather than unique and stable disorders. Studies have suggested that DES represents a disorder of loss of neural inhibition. Experimental work in both animal and human studies have found that inhibition of nitric oxide (NO) results in simultaneous contractions in the distal esophagus, a pattern that characterizes DES, while replacement of NO reverses the defect [19, 20].

In nutcracker esophagus, endoscopic ultrasound studies show that there is an incoordination between the contractions of the circular and longitudinal muscle layer [21]. This incoordination was reversed with atropine, suggesting a hypercholinergic state is important in pathogenesis [21, 22]. Both conditions also have coexisting GERD or visceral hypersensitivity [23, 24]. Treatment strategy thus usually involves first identifying whether GERD is present via pH monitoring, thereby identifying a need for anti-GERD therapy [25]. Medical therapy also includes the use of nitrates, calcium

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Table 22.1 Analysis of selected esophageal motility disorder treatment methods

Method of treatment	Associated disorders	Advantages	Disadvantages	Success
Acid suppression	DES, NE, NEMDs, SSc	Relieves GERD symptoms	May only treat GERD symptoms	Low success in children
Antibiotics	Caustic ingestion, CIIP, SSc			
Botox injection	Achalasia	Suitable for long-term use	May contribute to fibrosis at injection site	
Elemental diet	Caustic ingestion, EoE, DES, NE, SSc	Quick resolution of symptoms	Formulas not palatable	Compliance difficult for children
			Lower quality of life	
			Cost/insurance coverage	
Elimination diet	EoE, CIIP	Still allows for some food intake by mouth	Requires careful review of all food choices for allergens	Must continue elimination for long-term resolution
			Does not always indicate specific food allergen at fault	
Esophageal dilation	Achalasia, caustic ingestion, DES, EoE, NE	Highly effective when strictures are also present	Chest pain	Common treatment in adults
			Esophageal perforations	
Other surgical procedures	Achalasia, caustic ingestion, DES, HD, NE		Complications may further complicate disease	Usually successful with rare complications
Systemic or topical corticosteroids	EoE, SSc	Direct administration to eosinophilia (topical)	Low bioavailability	Satisfactory symptom resolution
		Variety of administration (swallowed or inhaled)	May not fully penetrate eosinophilia (topical)	High rate of symptom relapse upon discontinuation

channel blockers, and sildenafil, which allow prolongation of muscle relaxation, though esophageal function is further complicated when the LES becomes too relaxed due to medication [25–27]. Anxiolytics may be used in DES patients diagnosed with anxiety or depression [12, 14]. The use of visceral analgesics (tricyclic antidepressants, serotonin reuptake inhibitors) improved global symptom scores in individuals with esophageal contraction abnormalities and DES and has shown improvement in nutcracker esophagus as well [28]. Botox is being used increasingly for both conditions. A recent study examined 22 patients with DES or nutcracker esophagus that had primarily dysphagia and gave them blinded saline or botulinum toxin injections in a crossover study design. Results showed that symptom scores and weight loss improved after the botulinum injections, not the saline injections, and this benefit was sustained for over a year in almost half of the patients [29]. Medical and surgical approaches are intended to alleviate pain and decrease severity of symptoms [12]. Patients may undergo pneumatic dilation to relieve symptoms, but the procedure is not consistently effective because the balloon can be difficult to place. Surgery is usually reserved for those patients with dysphagia and hypertensive sphincter. Selecting a treatment option should be used based on bolus transit and manometry findings [13] (Table 22.1).

Eosinophilic Esophagitis

Eosinophilic esophagitis (EoE) is a condition in which the esophagus becomes inflamed due to infiltration by eosinophils. It is a clinicopathological disease characterized by clinical symptoms of esophageal dysfunction, detection of >15 eosinophils/HPF, and exclusion of other disorders associated with similar clinical, histological, or endoscopic features, especially GERD [30]. Other histologic features include eosinophil microabscesses, superficial layering of eosinophils to upper third to half of the squamous epithelium, and basal zone hyperplasia with the basal zone occupying more than 20 % of the epithelium [31–33]. Endoscopic features include linear furrowing, white exudates, specks, or nodules, circular rings, linear shearing/crepe paper mucosa with passage of endoscopy, and esophageal stricturing [31, 34–38]. Although none of these are pathognomonic for EoE, the finding of one or more, in the appropriate clinical context, is strongly suggestive of EoE.

The exact incidence and prevalence of EoE is likely underestimated given that the knowledge of, and screening for, EoE is increasing. Noel et al. reported an incidence of ~1:10,000 children per year in the Midwest United States occurring over a period from 2000 to 2003 [39]. In an analysis of a large administrative database, the period prevalence of EoE from 2009 through 2011 in the United States was estimated to be 56.7/100,000 persons [40]. EoE has a higher prevalence in males than in females; 16 studies identified 754 pediatric patients, 66 % of which were males [30]. It is postulated that 10 % of children with GER, unresponsive to acid suppression therapies, have EoE [41]. Overall, prevalence tends to be higher in individuals with a history of dysphagia and pre-diagnosed/existing cases of GERD, reflux esophagitis, and food impaction [42].

Symptoms experienced by patients differ by age, with adults experiencing dysphagia and food impaction [43–46]

and children experiencing feeding refusal or intolerance, GERD-like symptoms, failure to thrive, chest pain, emesis, and abdominal pain [46–49]. The difference in symptoms is attributed to pediatric patients being unable to verbalize what they are experiencing, as well as a longer disease duration leading to fibrosis [50]. This is reflected in endoscopic changes as disease course progresses, with features of EoE shifting away from those that reflect inflammation, such as plaques, toward those that reflect remodeling such as concentric rings, narrowing, and strictures [51].

Etiopathogenesis of the eosinophils remains unknown, but is thought to be related to allergen hypersensitivity, with inflammation resulting from repeated exposure to food and aeroallergens in genetically susceptible individuals [52–54]. Allergic responses have been strongly implicated in the etiology of EoE based on several lines of evidence. The majority of patients with EoE (50–80 %) [54] are atopic based on the coexistence of atopic dermatitis, allergic rhinitis, and/or asthma and the presence of allergic antigen sensitization based on skin prick testing or measurement of plasma antigen-specific IgE. Also, most patients improve on allergen-free diets, providing supportive evidence that antigen is eliciting the disease.

EoE is characterized by Th2-mediated inflammation. The activated Th2 response leads to the recruitment and activation of eosinophils and mast cells, which degranulate, releasing products that instigate tissue damage, remodeling, and fibrosis. IL-5, IL-13, and TGFβ1 are master regulators of EoE [55–58]. They can induce other pro-fibrotic agents in the lamina propria [59]. Mechanisms responsible for esophageal dysmotility associated with EoE are somewhat uncertain, though it is likely that esophageal remodeling is the molecular scaffold responsible. The bulk of remodeling changes occur in the subepithelial compartments [60]. Remodeling includes basal zone hyperplasia, epithelial–mesenchymal transition (EMT), fibrosis, angiogenesis, and smooth muscle hypertrophy/hyperplasia [61]. Tissue fibrosis results in decreased esophageal compliance, increased esophageal stiffness, smaller esophageal diameter, and increased smooth muscle mass with smooth muscle dysfunction. Complications, such as esophageal rigidity, dysphagia, food impactions, and esophageal strictures, seem to be secondary to tissue remodeling. There are limited techniques to evaluate and monitor for tissue remodeling and fibrosis. To date, studies have relied on radiographic and endoscopic surrogates to qualitatively assess degree of fibrosis and compliance of the esophagus [62]. Endoscopic ultrasound or computed tomography scan has confirmed that substantial thickening of the entire esophageal wall occurs in approximately 50 % of cases [63], whereas longitudinal muscle dysfunction with abnormal peristalsis has been identified on both ultrasound and manometry [64].

There are few studies utilizing high-resolution manometry (HRM) in EoE patients, particularly after treatment. Studies show that HRM is able to identify esophageal motility disorders in only some EoE patients, despite them having symptoms and eosinophils present on esophageal biopsies [65, 66]. The observed motility disorders resolve after successful treatment in almost all of these patients. Panesophageal pressurization and weak or failed peristaltic integrity are more often present in adult EoE patients than in healthy controls [66, 67]. This can also be seen in GERD patients. However, it was shown that a longer disease duration increased the prevalence of manometric abnormalities in EoE patients [67]. Similarly, studies in children show that both patients with EoE and GERD have findings of peristaltic dysfunction (i.e., failed peristalsis, aperistalsis, and esophageal spasm features) and lower distal contractile integral adjusted for esophageal body length, with patients with EoE having a higher prevalence of abnormal findings [68]. The same study also evaluated children with MII-pH and found that the great majority of EoE patients have a normal MII-pH profile, while patients with GERD have a markedly higher number of abnormalities picked up. Use of esophageal pressure topography yielded the same results—that abnormal esophageal motility was sometimes picked up in patients with EoE who were similar in frequency and type to patients with GERD and patients with EoE were more likely to have abnormal bolus pressurization patterns thought to be a reflection of reduced esophageal compliance [69].

The current tools of manometry and endoscopy lack the ability to test distensile properties of the esophageal wall, as the pressure–geometry relationship of the esophageal lumen cannot be measured. Kwaitek et al. demonstrated the utility of measuring esophageal body distensibility by high-resolution impedance planimetry (EndoFLIP, endoscopic functional luminal imaging probe) to calculate multiple adjacent cross-sectional areas (CSAs) within a cylindrical bag while simultaneously measuring intraluminal pressure during controlled volumetric distension [62]. Patients in whom EoE was confirmed by biopsy were found to have decreased distensibility of the esophageal body and gastroesophageal junction compared with healthy controls. Neither mucosal eosinophil count, age, gender, nor current PPI treatment predicted this limiting caliber of the esophagus. The same group later investigated the EndoFLIP as a tool to predict the risk of food impaction in EoE [70, 71]. They concluded that EoE patients had a lower maximal reachable CSA, termed the distension plateau, than controls and that this measure predicted the risk of food impaction.

EoE is a chronic and progressive disease. If left untreated, complications, such as food impaction, esophageal stricture, narrow-caliber esophagus, and esophageal perforation, are common. Therefore, once the diagnosis is confirmed, it is important to treat the eosinophilic inflammation not only to control the presenting symptoms but also to preserve the morphological and functional integrity of the esophagus. Besides medications that are geared toward decreasing inflammation, diets avoiding culprit foods is an important therapeutic option [30]. Systemic steroids, while effective, have the downside of

systemic symptoms. In a retrospective study of 20 children, oral viscous budesonide mixed with Splenda to create a topical steroid slurry resulted in a 3–4-month resolution or improvement of symptoms in 85 % of patients [72]. This provides a suitable alternative to children who have difficulty with inhalers. Dietary options come in three forms: elemental diet, elimination diet that is determined by identifying trigger foods, or a six-food elimination diet that eliminates the six most common allergens. Esophageal dilation is reserved for symptomatic esophageal strictures.

Collagen Vascular Disorders

Among collagen vascular disorders, scleroderma is the most severe and commonly manifests in the gastrointestinal tract. Other collagen vascular disorders with esophageal manifestations are systemic lupus erythematosus (SLE), mixed connective tissue diseases (MCTDs), Sjörgen's syndrome, and rheumatoid arthritis. Scleroderma is the hardening of tissues resulting from an autoimmune response attacking the body. Systemic scleroderma (SSc) is characterized by remarkable collagen deposition in body tissue, especially the esophagus. SSc affects esophageal tissue and motility in 75–90 % of adult cases [73, 74]; pediatric studies indicate much lower prevalence [75, 76]. In a multicenter study, Foeldvari et al. reported 65 % (88/135) of pediatric SSc patients presented GI tract involvement; only involvement with the skin, joints, and Raynaud's phenomenon preceded GI tract [77]. Of those 135 cases, under 50 % ($n=63$) involved the esophagus [77].

Esophageal smooth muscle becomes atrophied and replaced by fibrous tissue leading to severe motility disturbance of the distal esophagus. A study of SSc revealed that childhood onset is sometimes preceded by trauma in the area of deposition, a unique phenomenon compared to adult cases of scleroderma [76]. It is postulated that trauma releases the neuropeptide ET-1, stimulating collagen synthesis in fibroblasts [76]. In the presence of SSc, esophageal manometry reveals an incompetent LES, low-amplitude peristalsis in the distal esophagus, and a normal proximal esophagus which is made of striated muscle of the esophagus [73]. The retrograde movement of gastric contents, related to LES pressure, exposes the esophagus to acidity, which can compromise peristalsis. Frequent contact between acidic gastric contents and esophageal mucosa degrades tissue quality; esophagitis, bleeding, and strictures are other known complications. However, studies have noted that many who experience reflux secondary to SSc can be asymptomatic [73, 78]. In a study by Weber et al., 15 pediatric patients with scleroderma or mixed connective tissue disease underwent 24-h pH monitoring. While 85 % had an elevated number of reflux events and 50 % had reflux events lasting greater than 5 min, only three patients had clinical symptoms [78]. Aside from manometry, barium esophagram, 24-h ambulatory pH, and endoscopy are also used to diagnose the extent of esophageal disturbance secondary to SSc [73].

Common symptoms of SSc with esophageal involvement are dysphagia, chest pain, weight loss, food impaction, and early satiety [73, 79]. Weber et al. reported reflux events in over 60 % of pediatric patients with SSc [78]. Overall mortality for SSc with esophageal involvement is very rare; death is usually a consequence of multisystem involvement [76, 77]. Treatment of SSc primarily involves immunosuppressants (prednisone, methotrexate, mycophenolate mofetil, tumor necrosis factor-alpha, cyclophosphamide) [76, 80]. However, the suspected effect of immunosuppressants on fertility must be further evaluated in the pediatric population [81–83]. Gunawardena and McHugh suggest proton pump inhibitors, bulking agents, nutritional supplements, and antibiotics as additional treatment options [79, 84]. More investigation into effective treatment of pediatric collagen vascular disorders with esophageal manifestation is needed.

Chronic Idiopathic Intestinal Pseudo-obstruction

Chronic idiopathic intestinal pseudo-obstruction (CIIP) is a rare primary disorder that involves the entire gastrointestinal tract (see Chap. 24). Esophageal involvement is very common [85]. Non-idiopathic intestinal pseudo-obstruction is usually secondary to systemic, metabolic, genetic, or mitochondrial etiologies. CIIP is often diagnosed during infancy and childhood, and symptoms are usually both severe and frequent at onset. Patients with esophageal involvement present with clinical symptoms of GER, dysphagia, nausea, vomiting, and weight loss [86, 87]. Dysphagia, however, is usually a chief complaint when CIIP is secondary to another disorder.

Upper GI, endoscopy, manometry, and full thickness biopsies are used to diagnose CIIP. Abnormal manometry is intermittent, and abnormalities include uncoordinated (neuropathic) or low-amplitude (myopathic) contractions with swallowing [86]; these findings are more common than aperistalsis. Decreased LES pressure is also a common clinical finding. Pharmacologic treatment of CIIP is similar to that of other esophageal motility disorders, involving antiemetics, prokinetics, and antispasmodics. Antibiotics are suggested to reduce bacterial growth, which may also benefit abdominal pain, distention, and diarrhea [86].

Hirschsprung's Disease

Lack or poor formation of the enteric nervous system defines Hirschsprung's disease (HD) (see Chap. 25). Though primarily a disease of the small and large bowel, HD is occasion-

ally associated with abnormal esophageal motility indicated by poor peristaltic wave propagation [88]. Staiano et al. examined esophageal involvement in children with HD, in comparison to those with idiopathic megacolon and healthy controls with no esophageal or colonic diseases. Abnormalities in the amplitude and frequency of distal esophageal body contractions were significantly higher in HD patients than other groups [89]. The severity of HD in this group was unrelated to esophageal involvement. Another study evaluated if upper GI dysmotility in HD patients persists into adulthood [90]. Sixteen adult HD patients and 17 controls evaluated via antroduodenal and esophageal manometry revealed increased contractile activity of the small bowel during fasting and postprandially in HD adults.

Caustic Ingestion

Caustic ingestion of harmful substances is a common accident among young children, especially in developing countries. Common signs and symptoms include salivation, oropharyngeal burns, vomiting, bleeding, epigastric and retrosternal pain, and malignant transformation [91, 92]. Esophageal burns, though less common than oropharyngeal, are associated with fibrosis of deep muscle tissue which impairs normal motility. Acids and alkalis produce different types of tissue damage. Esophageal motility studies report low-amplitude and nonperistaltic contractions in patients with dysphagia and stricturing [93–95].

Ineffective Esophageal Motility

Ineffective motility of the esophagus has evolved from being included in an initial description of nonspecific esophageal motility disorder (NEMD) to a more precise terminology establishing it as a separate entity. The unifying feature of swallows contributing to the diagnosis of ineffective esophageal motility (IEM) is poor bolus transit in the distal esophagus. In 2001, using conventional manometry, Spechler and Castell defined IEM as having low or normal esophageal sphincter pressure, normal LES relaxation, and greater than 30 % low-amplitude waves characterized by the following: wave amplitude <30 mmHg, peristalsis that does not travel the length of the esophagus, simultaneous contraction <30 mmHg, or aperistalsis [96]. Tutuian and Castell indicated in 2004 that patients with ≥50 % ineffective wet swallows (<30 mmHg) are more likely to have abnormal bolus transit [97]. Blonski et al. showed that this definition was more frequently associated with esophageal symptoms (dysphagia and heartburn) and abnormal bolus transit compared to those who had only 30–49 % ineffective swallows [98]. The Chicago Classification by HRM defines IEM as DCI <450 mmHg s cm with ≥50 % ineffective swallows. No distinction need be made between failed swallows and weak swallows [99]. IEM is the most common abnormality on esophageal manometry, with an estimated prevalence of 20–30 % [100]. With the use of HRM to define IEM, the prevalence of IEM has increased. Boland et al. performed HRM on 350 adult patients referred for esophageal function testing between August 2012 and May 2013 [101]. Thirty-one percent of patients had IEM compared to 21 % 10 years prior, when 350 patients had been evaluated via MII-EM.

Patients with IEM present with various complaints. Analysis of 228 IEM patients in a study showed dysphagia in 25 % of patients, cough in 15 %, chest pain in 13 %, heartburn in 12 %, and regurgitation in 12 % [102]. Among patients with dysphagia, bolus transit was defective in 89 %. The presence of dysphagia with defective bolus transit in patients with severe IEM was also shown in 2008 [103]. IEM thus appears to subdivide into two groups, a more severe form that manifests with dysphagia and is associated with a more defective bolus transit and a milder form of which the clinical significance is not very clear. The association between IEM and GERD is well documented, and IEM is more prevalent in patients with more advanced reflux disease. Multiple studies showed esophageal peristaltic dysfunction was increasingly prevalent with more severe GERD presentation, from nonerosive reflux disease (NERD) to erosive esophagitis (ERD) and Barrett's esophagus [104–107]. It has not yet been determined whether IEM is a rare primary disorder or merely secondary to increased acid exposure.

Currently there is little data regarding IEM in the pediatric population. In infants with ALTE, prolonged spontaneous respiratory events are associated with ineffective esophageal motility characterized by frequent primary peristalsis and significant propagation failure, thus suggestive of dysfunctional regulation of swallow–respiratory junction interactions [104].

Nonspecific Esophageal Motility Disorders

Nonspecific esophageal motility disorders (NEMDs) capture those cases with irregular manometry, but not characteristic of an established disorder [1, 12, 108]. Criteria for NEMDs are ≥30 % of wet swallows with non-transmitted or low-amplitude contractions or at least one of the following contraction abnormalities: triple-peaked contraction, retrograde contraction, prolonged-duration peristaltic waves (>6 s), or isolated incomplete LES relaxation (>8 mmHg) [108]. Low-amplitude contractions are thought to be the most common manometric finding [109]. NEMDs differ from achalasia in that with swallows, there are intermittent normal and abnormal peristaltic waves; complete lack of peristalsis is characteristic of achalasia. Additionally, NEMDs involve low-amplitude

waves, whereas DES typically involves high-amplitude pressure waves. Despite these notably distinct symptoms, it is suggested that NEMDs may be an early disease state of achalasia and DES [109]. Naftali et al. reported a minority of patients who progressed from NEMD to achalasia or DES noted during a repeat manometry procedure. In a retrospective study following 43 patients with NEMD over 4 years, 28 patients had repeat manometry for persistent symptoms, and among them, 15 patients had progressed to achalasia. Almost all of them were <46 years old, suggesting that an early age of onset is predictive of disease progression [110].

Common symptoms are dysphagia, vomiting, chest and epigastric pain, and food impactions [2, 12, 25]. NEMDs are much less common than other primary esophageal motility disorders, such as achalasia and DES. In a cohort of 154 children with upper GI symptoms, 30 were not diagnosed with GER. Of those 30 patients, 43 % ($n = 13/30$) were found to have NEMDs, representing 8 % of the entire cohort [111]. In addition to normal esophageal pH, many of those diagnosed demonstrated normal endoscopic appearance and esophageal histology; thus, clinical findings (i.e., food impaction) are of great significance with regard to NEMDs [111]. Palliative treatment method for NEMDs usually involves antispasmodic agents, prokinetics, antacids (where GER is present), and/or PPIs [2, 112]. Improvement with these methods is variable; some may even improve without pharmacologic intervention [111].

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Gastric Motor Disorders

23

John M. Rosen and Miguel Saps

The motor function of the gastrointestinal tract is a complex interaction of stimulus and effect. Normal function results from the coordination of various processes in response to internal and external stimuli including ingestion of food. Effective stomach filling and emptying relies on the interplay of the autonomic nervous system, neurotransmitters, enteric smooth muscle, sensory afferent nerves, and other intrinsic and extrinsic factors. Interruption of any of these components may result in dysmotility. Gastroparesis is a disorder of the stomach in which emptying of gastric contents is delayed in the absence of mechanical obstruction. It occurs in up to 4 % of adults and can result in significant disability. Dumping syndrome is another symptomatic disorder related to rapid gastric emptying and may be equally debilitating.

Gastroparesis

Adult studies demonstrate that gastroparesis is common and more frequent in females and that hospitalizations related to the disorder have been increasing [1]. Studies conducted in two tertiary care centers found that 25–62 % of children who underwent 4-h scintigraphy had abnormally delayed gastric emptying [2–4]. In children, gender predominance of gastroparesis seems to vary by age. In infancy, gastroparesis is more common among boys, has a similar prevalence in both genders in children, and predominates in females in adolescence [5]. Differences in etiological factors between children of various ages and between children and adults may explain these findings.

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Gastroparesis may result from multiple pathophysiological mechanisms including altered fundic receptive relaxation, decreased antral contractility, and incoordination of gastric emptying and duodenal contractions. Signs and symptoms of gastroparesis can wax and wane over time and include bloating, nausea, early satiety, abdominal pain, vomiting, failure to thrive, and weight loss. The severity of symptoms may vary from patient to patient ranging from minimal and tolerable to severe and debilitating.

The relationship between gastroparesis and its separation from functional dyspepsia remains an area of controversy and active investigation. Symptoms of gastroparesis are not specific and overlap with those of functional dyspepsia. Abdominal pain may be present in both disorders; however, it rarely represents the most bothersome symptom in patients with gastroparesis. Nausea is present in 29 % of children with functional dyspepsia [6] and 77 % of children with gastroparesis [2].

Abnormalities of gastric electrical and motor activity [7] may be present in both disorders, and up to 2/3 of children with functional dyspepsia may have delays in gastric emptying [8]. The recognition of this overlap is important at the time of recommending treatment, for the understanding of the pathophysiology of both disorders and for the identification of specific cohorts in research studies.

Gastroduodenal motility depends on the prandial state, food composition, presence and type of inflammation, distal intestinal motor function, and both motor and autonomic neural input. Gastroduodenal function can be measured with a variety of tools including scintigraphic emptying tests, exhaled breath tests, gastric barostat, antroduodenal manometry (ADM), ultrasound, and electrogastrography (EGG) as well as newer studies including single-photon emission computed tomography (SPECT) and the wireless motility capsule (WMC). Each test measures related, but different, aspects of physiology including compliance, accommodation, contractility, coordination, and propagation. Evaluation by upper gastrointestinal endoscopy and biopsy has a relatively low yield in patients with gastroparesis, but may remain an important part of evaluation for other disorders [9].

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The diagnosis of gastroparesis is determined by the demonstration of delayed gastric emptying with 4-h gastric scintigraphy, the current gold standard (Fig. 23.1). Gastric scintigraphy should be performed with a standardized meal and using normative emptying values (gastric retention of >90 % at 1 h, >60 % at 2 h, and 10 % at 4 h) as recommended by the Society of Nuclear Medicine and the American Neurogastroenterology and Motility Society [10]. Normative emptying values were established based on data in adults and have been adopted in pediatrics. Although no specific studies have been conducted to validate these values in children, a meta-analysis of patients of a wide age spectrum (premature neonates to adults) found no age-dependent effect on gastric emptying [11]. The importance of completing a 4-h test was demonstrated in adult and pediatric studies. A review of 1500 adult patients found frequent "false negatives" in studies of less than 4 h [12]. A pediatric study has also shown that the use of 4-h testing has a higher sensitivity than studies of shorter duration [3]. Thus, the use of 4-h testing and a normative standard meal is strongly recommended. Despite these recommendations, many centers continue to conduct studies with a wide variety of protocols and length of study. Modifications to the protocol may be justified in special circumstances. The solid meal is not suitable for exclusive enteral formula-fed patients, and neonates and young or small children are frequently not able to complete the adult-size meal [4]. The protocol may also be difficult to complete for those in whom an egg sandwich results in intolerable gastrointestinal symptoms

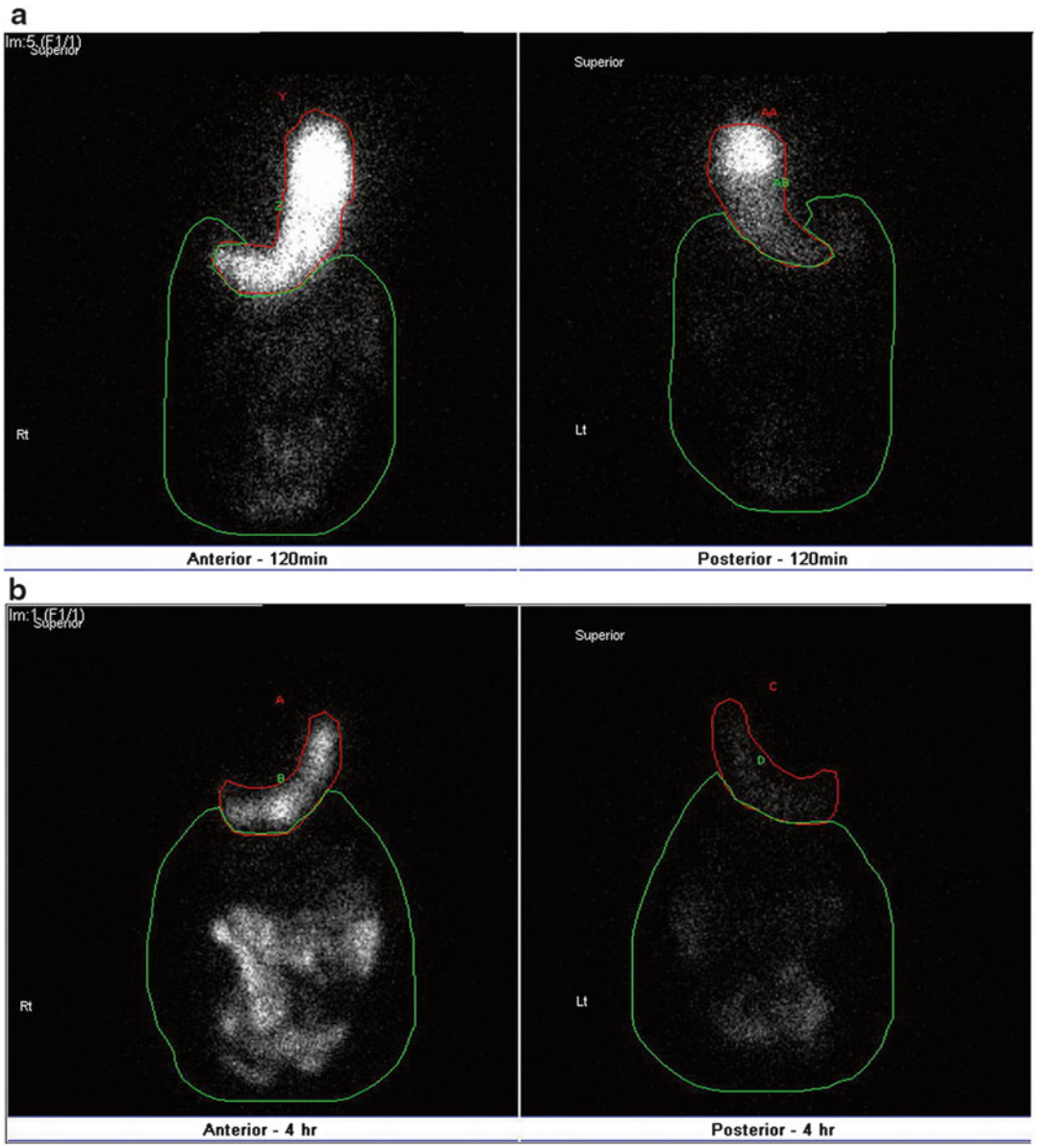

Fig. 23.1 Gastric emptying scan showing delayed gastric emptying with greater than 60 % and 10 % Tc 99 m sulfur colloid activity in the stomach at 2 h and 4 h, respectively

or who are allergic to components of the meal. Alternative protocols have been developed to overcome the limitations of the solid food-based nuclear medicine testing and to study other aspects of the stomach function. Liquid emptying studies can be used in younger children, but the results of liquid emptying cannot be automatically extrapolated with studies of gastric emptying using a solid meal. In the fed state, gastric emptying varies with food composition, including caloric content, osmolality, temperature, and the physical characteristics of the meal. As liquids do not need to be grinded prior to emptying, they have a faster emptying time than solids and follow a different emptying curve. A study in adult healthy volunteers proposed that a liquid nutrient meal can be used as an alternative to the standard solid meal. The study found that the *t*-1/2 gastric emptying of a liquid nutrient meal (Ensure Plus®) was similar to an egg sandwich meal [13]. A pediatric study has proposed normative values using liquid gastric emptying (200 mL of strawberry flavored milk and a caloric content of 112 kcal) measured by the [13] C-acetate breath test [14]. Liquid emptying times in this study were independent of age, gender, and BMI. The use of the isotope breath test is an attractive method to measure gastric emptying in children due to its simplicity and low risk.

The wireless motility capsule (WMC) is increasingly used to measure gastric emptying in children and adults. The American and European Neurogastroenterology and Motility Societies have recommended consideration of WMC testing in "the assessment of: (a) gastric emptying and regional and whole gut transit time in individuals with suspected gastroparesis, symptoms of upper GI dysmotility, or suspected alterations of GI motility in multiple regions" as well as for other indications [15, 16]. The nondigestible WMC has a distinct emptying pattern. Studies have shown that when given with a solid meal, the WMC empties from the stomach with the return of phase III MMCs after the emptying of the solid-phase meal occurs [17]. Several pediatric studies have used ultrasound to assess gastric emptying in children of different ages including preterm neonates [18, 19]. Ultrasound requires no radiation and the equipment is easily available; however, it requires high skill and is operator dependent. Therefore, different tests can be employed to study the mechanical properties of the stomach including gastric emptying. An in-depth discussion of the different methods used to study gastric emptying is provided elsewhere in this book.

Etiology

Etiology of gastroparesis in children is most often idiopathic or postviral. Together, both have been associated with up to 70% of cases of gastroparesis in children [20]. Surgery and medication effects are the next most common factors implicated in pediatric gastroparesis. Multiple other etiological factors have been described in children of various ages (Table 23.1).

Table 23.1 Etiology of gastroparesis in children

Idiopathic
Postinfectious
CMV, EBV, *rotavirus*, *mycoplasma*
Postsurgical
Fundoplication, vagotomy, partial gastrectomy
Other thoracic and abdominal surgeries
Metabolic
Type 1 DM, type 2 DM
Hypothyroidism, hyperthyroidism, hypopituitarism, Addison's disease
Dysautonomic
Amyloidosis, toxins, infection (Chagas disease, HIV), hereditary disorders, immune-mediated and autoimmune disorders, paraneoplastic syndrome
Immune mediated
Celiac disease, inflammatory bowel disease, cow's milk protein allergy, autoimmune neuropathy
Medication related
Anticholinergics, opioids, tricyclic antidepressants, proton-pump inhibitors, H2 receptor antagonists, antacids, sucralfate, octreotide, beta-adrenergic agonists, calcium channel blockers, levodopa
Others
Hirschsprung disease
Constipation
Muscular dystrophy
Critical illness
Mitochondrial disease
CNS disease
Prematurity
Caustic ingestion
Marijuana

Development

Intestinal development continues to occur during the third trimester of gestation, and interruption of this development, most commonly by preterm birth, may result in symptomatic disorders. Normal gastric liquid emptying, both electrical rhythm and motor activity, has been demonstrated in 32–34-week gestation infants [21, 22]. Gastric electrical activity and motor function continues to develop postnatally with enteral nutrition stimulating continued maturation of intestinal motor function [23]. Gastric electrical activity develops further in the first decade of life before achieving normal adult patterns [24].

Postinfectious

In children, gastroparesis has been reported following rotavirus, EBV, CMV, and *mycoplasma* infection [25–27]. An infectious etiology is suspected frequently in the course of clinical care of a child with gastroparesis, but the infecting

agent is rarely identified. Postinfectious gastroparesis is suspected when a previously healthy individual has acute onset of gastrointestinal symptoms characteristic of infectious enteritis—nausea, vomiting, diarrhea, fever, or abdominal pain. At presentation, the clinical findings of children who develop postinfectious gastroparesis can be mild or severe and identical to other children with acute gastroenteritis. However, in children with gastroparesis, the gastrointestinal symptoms persist for months to years. Long-term outcomes are excellent, with resolution of symptoms typically between 6 months and 2 years [25, 28]. Evaluation of adults with gastroparesis demonstrates abnormalities of enteric neurons and interstitial cells of Cajal (ICC), and it is hypothesized that viral infections could cause such injury. Although several types of infection can result in gastroparesis, not every infectious agent that affects the stomach is associated with delayed emptying. A study on adult patients found a lower prevalence of *Helicobacter pylori* infection in patients with gastroparesis than controls [29].

Diabetes Mellitus

Diabetes mellitus is an uncommon cause of delayed gastric emptying in children. In contrast, up to 30% of adults with type 2 diabetes mellitus (T2DM) have gastroparesis [30]. Poor glucose control, vagal parasympathetic dysfunction, and depletion/dysfunction of ICC and gastric enteric neurons are postulated to alter gastric physiology in diabetics [31]. Relaxation of the fundus and gastric capacity are decreased in diabetics. Uncontrolled diabetes may cause gastric dysrhythmias; ineffective contractions of the fundus, corpus, and antrum; and pyloric hypercontractility [32–34]. Similar to adults with T2DM, children with type 1 diabetes mellitus (T1DM) may have antral hypomotility, gastroparesis, and gastric electrical dysrhythmias [35, 36]. A study comparing children with T1DM to children with chronic dyspepsia or chronic constipation (but no T1DM) identified lower serum motilin concentrations among diabetics, but found no difference in autonomic function, gastric emptying, or total intestinal transit time [37]. Other studies found delayed gastric emptying [35, 36], autonomic dysfunction [38], and even rapid gastric emptying [39], underscoring the need to study the gastric function of T1DM patients who present with gastrointestinal symptoms to establish individual therapeutic plans.

Dysautonomia

Autonomic peripheral neuropathies may occur secondary to diabetes mellitus, primary and hereditary amyloidosis, toxins (organic solvents, vincristine), infection (Chagas disease, HIV), hereditary disorders (hereditary and sensory autonomic neuropathies, Fabry disease, Allgrove syndrome), immune-mediated and autoimmune disorders (Guillain-Barré syndrome, systemic lupus erythematosus, myasthenia gravis), and paraneoplastic syndrome [40]. Symptoms typically affect multiple organs with variable severity although upper gastrointestinal symptoms are common.

Autoimmune Neuropathy

Autoimmune gastrointestinal dysmotility presents with subacute onset of autonomic dysfunction. Clinical findings may be generalized or limited to the gastrointestinal organs and include nausea, vomiting, and/or gastroparesis. Involvement of the esophagus (including achalasia), pyloric stenosis, intestinal pseudo-obstruction, and anal spasm have been reported [41]. A case series of adults with ganglionic acetylcholine receptor antibodies found gastroparesis, constipation, anhidrosis, dry eyes and dry mouth, a neurogenic bladder, and orthostatic hypotension [42]. Although there were few patients, significant variability in disease severity and the potential for chronic duration were demonstrated. A case series screening sera of patients with autoantibodies and gastrointestinal disease identified 12 patients with delayed gastric emptying [41]. The patients had antibodies to ganglionic acetylcholine receptor [7], voltage-gated calcium channels N-type [3], thyroperoxidase [3], thyroglobulin [3], glutamic acid decarboxylase 65 kDa isoform [2], islet cell antigen 512 [2], antineuronal nuclear autoantibody, type 1/anti-Hu [1], and muscle acetylcholine receptor [1].

Disturbances in gastrointestinal motility including delayed esophageal, gastric, and small intestinal transit, as well as delayed or accelerated colonic transit, have been described in patients with celiac disease [43, 44]. A study on adult celiac disease patients found delayed gastric emptying that normalized after 1 year of gluten-free diet (GFD) [45]. A study in children with celiac disease showed near-complete resolution of antroduodenal dysmotility after 6 months of GFD [46]. However, another study in adult patients found altered antroduodenal manometry in the fasting and fed state even in those adherent to a GFD [47]. Persisting autonomic dysfunction, peripheral neuropathy, and antineuronal antibodies found in a series of celiac disease patients on GFD could explain these findings [48].

Gastric emptying is delayed in some patients with inflammatory bowel disease, and prolonged emptying times may be associated with disease activity through a GLP-1-mediated pathway [49]. Interestingly, the location of disease activity does not necessarily correlate with altered gastric motility. Gastrointestinal neurohumoral mediators (including GLP-1 and CCK) may be altered even in distal small intestinal or colonic inflammation and associate with gastric emptying delay [50]. Further, as in treated celiac disease, gastroparesis may persist in patients even with inactive inflammatory bowel disease [51, 52].

Central Nervous System Disorder

Children with chronic illnesses including central nervous system disorders have a high incidence of gastric dysrhythmias, gastroparesis, and abnormal antroduodenal motility [53–55]. In one study, 31/50 children had gastric dysrhythmias [53], while in another study all children had abnormal antroduodenal manometry and half of them had delayed gastric emptying of liquids [54]. Although not all children with central nervous system disorders have abnormalities of gastrointestinal motility, the possibility of gastroparesis, gastroesophageal reflux disease, feeding disorders, and constipation should always be considered.

Mitochondrial Disorder

Gastrointestinal manifestations of mitochondrial disease are varied and complex [56]. Several case series identify gastroparesis in the setting of specific mitochondrial disorders. Eighteen of 26 children with mitochondrial disease had delayed gastric emptying with delays persisting in most despite prokinetic therapy [57]. Four patients with upper gastrointestinal symptoms consistent with gastroparesis were identified to have 3243A>G mtDNA mutation in specific stomach regions [58]. This mutation is implicated in mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS). Three of the patients were further studied and found to have abnormal EGG and gastric emptying, although gold-standard scintigraphy was not used. Six children with defects in mitochondrial electron transport chain enzymes of oxidative phosphorylation (OXPHOS), but no specific mtDNA mutation, were found to have abnormal antroduodenal manometry indicative of neuropathy, and four had delayed gastric emptying [59].

Hirschsprung Disease

Although Hirschsprung disease (HD) is generally considered a disorder of the lower gastrointestinal tract, abnormalities of upper intestinal motility have been identified years after repair. Specifically, esophageal body abnormalities were found on manometry of 12 children with HD [60]. Similar findings were identified in 11 children with total colonic aganglionosis who had abnormalities in esophageal body contractions and propagation, but generally preserved UES and LES tone [61]. Antroduodenal manometry in these HD patients found a mix of abnormal propagation, distribution, or occurrence of phase III activity in the MMC.

Gastric emptying function is also affected in children with HD. HD patients have significantly longer total gastrointestinal transit times than controls even after surgical repair. In only few cases does the delay in gastrointestinal transit relate to prolonged colonic transit [62]. Patients with HD had longer gastric isotope retention than controls at 60 and 90 min, with 12/21 HD patients having >60 % retention at 60 min (>2SD from mean). Although HD patients frequently reported persistent vomiting and/or abdominal distension, the symptoms did not predict gastroparesis. Similarly, the frequency of bowel movements had poor correlation with gastric emptying times. Forty percent of HD patients with normal bowel frequency had delayed gastric emptying.

Food Allergy

Infants sensitized to cow's milk (cow's milk protein allergy—CMPA) had significant gastric electrical dysrhythmias and delayed gastric emptying measured by electrical impedance tomography when compared to controls with gastroesophageal reflux [63]. A positive food challenge in children identified resultant electrogastrographic changes and mast cell degranulation in proximity to gastric nerve fibers [64]. In children with FD, increased antral mast cell density is associated with slower gastric emptying [65]. Gastrointestinal eosinophils and mast cells, in animal and human studies, are increasingly associated with alterations in gastric motor and electrical function [66].

Postsurgical

Gastroparesis may follow specific surgical procedures including fundoplication, bariatric surgery, and heart or lung transplantation [67]. Although purposeful vagotomy is infrequently performed, inadvertent vagal injury may occur during the course of other upper abdominal or thoracic procedures. Gastroparesis-related symptoms following vagal injury can improve with time, possibly due to enteric nervous system adaptation or vagal nerve reinnervation [67]. Fundoplication may result in accelerated or delayed gastric emptying, underscoring the complex interplay of factors associated with surgery. Multiple pathophysiological mechanisms may result in abnormal function following surgery. Antireflux procedures may affect sensorimotor function of the proximal stomach. Motor abnormalities that have been most frequently described in patients with fundoplication include alterations in antral peristalsis and receptive relaxation [68].

Other Factors

Many other factors are related to delays in gastric emptying. In children, constipation is often associated with upper gastrointestinal symptoms (including nausea) [69] possibly through the reflex inhibition (cologastric brake) of upper gastrointestinal motor activity. Constipated dyspeptic children

have more frequent delays in gastric emptying than non-constipated dyspeptic subjects, and their gastric emptying time improves after osmotic laxative treatment [70]. Activation of the cologastric brake may explain delays in gastric emptying associated with both rectal distension [71, 72] and voluntary suppression of defecation [73].

Endocrinopathies including hypo- and hyperthyroidism, hyperparathyroidism, Addison's disease, and hypopituitarism have been associated with gastroparesis. Myopathies including myotonic dystrophy and Duchenne muscular dystrophy are associated with severely symptomatic gastroparesis [74, 75].

Critically ill patients frequently exhibit severe gastroparesis which may be exacerbated by endogenous mediators, sepsis, mechanical ventilation, and medications. Over 50 % of mechanically ventilated critically ill adults have delays in gastric emptying [76], potentially increasing morbidity and mortality due to inability to administer adequate enteral nutrition. Multiple potential pathophysiologic mechanisms of ICU-associated gastroparesis have been explored including the roles of cholecystokinin, secretin, oxyntomodulin, GLP-1, GLP-2, pancreatic polypeptide, and peptide YY [77].

Psychological stress also has effects on electromechanical function. Experimentally induced stress has been shown to increase symptoms and inhibit normal postprandial EGG responses in some, but not all, studies [78, 79]. Stress is further shown to impair accommodation and to delay gastric emptying [80]. The stress effect on gastric emptying appears to be mediated at least in part via CRH [81].

Ingestions of caustic substances, medications, and marijuana have also been related to delays in gastric emptying. Although patients with caustic ingestion and chronic injury did not demonstrate symptoms of gastroparesis, studies have shown that the orocecal transit time [82] and scintigraphic gastric emptying [83] were delayed. Multiple medications including anticholinergics, opioids, tricyclic antidepressants, proton-pump inhibitors, H2 receptor antagonists, antacids, sucralfate, octreotide, beta-adrenergic agonists, calcium channel blockers, and levodopa can lead to delayed gastric emptying [84–86]. Endocannabinoids exert multiple effects on enteric neurons that may inhibit neuronal activity, synaptic transmission, and axonal mitochondrial transport [87, 88]. Delta-9-tetrahydrocannibinol (THC) slows gastric emptying in adults suggesting putative antiemetic effects are centrally mediated rather than related to alterations in gastric motor function [89].

Eating disorders also have a variety of potential gastrointestinal manifestations including gastroparesis [90]. Patients with anorexia nervosa have increased gastric dysrhythmias [91] and increased antral distension during meals with maximal dilation reached more quickly than controls [92]. Many case reports suggest the association of gastroparesis in anorexia [90]. Severity of malnutrition may be associated with gastroparesis in anorexia nervosa [92], although the relation of body weight to gastroparesis is unclear given contradictory data. Treatment of anorexia nervosa with refeeding may improve gastric emptying time [92, 93].

Patients with rumination syndrome are demonstrated to have normal EGG, scintigraphic gastric emptying, and MMCs on antroduodenal manometry [94]. However, rumination syndrome is at times related to gastroparesis through "conditioned vomiting" that can occur in the setting of delayed gastric emptying [95].

Treatment

Treatment of gastroparesis includes a variety of pharmacologic, interventional, and complementary therapies including prokinetic agents, pyloric botulinum toxin injection, implanted gastric neuromodulator, acupuncture, and herbal substances. Importantly, symptom resolution correlates very weakly with diagnostic measures of gastric emptying including 4-h scintigraphy.

Prokinetic agents effective for gastroparesis include serotonergic agonists, dopaminergic antagonists, and antibiotics. Cisapride [96] and tegaserod [97] are serotonergic agonists found to be efficacious in the treatment of gastroparesis, but are currently not available (aside from compassionate use) in the USA due to an increased risk of cardiac side effects. Metoclopramide and domperidone are dopamine antagonists with gastric prokinetic effects. However, the use of metoclopramide has declined in pediatric patients secondary to an FDA warning related to the risk for tardive dyskinesia with prolonged use. Domperidone does not have the same central nervous system risks, but in the USA is available only for compassionate use due to risk of cardiac dysrhythmias. Bethanechol, a muscarinic agonist, also stimulates gastric contractions [98]. Erythromycin, a macrolide antibiotic, activates motilin receptors in the stomach and small intestine, increases antral contraction amplitude and frequency, and induces phase III MMCs [99, 100]. Azithromycin, a related macrolide antibiotic, may also be useful for treatment of gastroparesis [101]. Other motilin receptor agonists [102], acylghrelin agonists [103], as well as other novel agents [104] are being investigated for treatment of gastroparesis, but are not frequently utilized in clinical care of pediatric patients.

Endoscopic pyloric botulinum toxin A injection has been used in children with gastroparesis refractory to prokinetic therapy [105]. Botulinum toxin was shown to be effective in approximately 2/3 of patients; however, the effects are generally transient and limited to several months' duration. Neuromodulation with the implanted gastric electrical stimulator was shown effective for symptom reduction in a series of pediatric patients with gastroparesis and dyspepsia [106] and is increasingly used for patients nonresponsive to medical

therapy. The mechanism of action of gastric stimulation is not completely understood. Low-frequency, high-energy stimulation is thought to entrain the gastric slow wave, increase slow-wave amplitude, and improve gastric emptying in adults with gastroparesis [107]. High-frequency, low-energy stimulation, such as that used in recent clinical trials [108], is shown to increase slow-wave propagation velocity, enhance the amplitude of postprandial slow waves [109], and lessen sensitivity to gastric distension [110], but does not improve gastric emptying rate [109].

Alternative therapies including acupuncture additionally were found to be effective in select adult gastroparetics [111–113], but large-scale and pediatric studies are yet to be performed. Ginger [114, 115] and peppermint oil [116] enhance gastric emptying, but their effect on upper gastrointestinal symptoms remains unclear.

Given the interaction between the stress response, visceral hypersensitivity, and electromechanical dysfunction, treatment of stress and anxiety may have a role in the management of gastroparesis. Interventions effective in children with chronic GI symptoms, but not necessarily gastroparesis, include cognitive behavioral therapy, gut-directed hypnotherapy [117], yoga [118], and biofeedback-assisted relaxation therapy (BART) [119]. An in-depth discussion of diagnostic testing and therapeutic options is provided in other chapters of this book.

Dumping Syndrome

Dumping syndrome is a disorder of postprandial gastrointestinal and vasomotor symptoms related to rapid gastric emptying. Rapid gastric emptying results in delivery of an osmotic load to the small intestine with accompanying fluid shifts, as well as nutrient delivery and subsequent disordered glucose regulation. Dumping syndrome may be idiopathic, iatrogenic, postinfectious, or related to diabetes mellitus. Classically it was identified after surgical procedures of the upper GI tract including fundoplication in children and gastrojejunostomy, pyloroplasty, and Roux-en-Y bypass in children and adults. It is reported in up to 30 % of children undergoing fundoplication [120], 35 % of adults with CVS, 13 % with diabetes mellitus, and 10 % with IBS [121].

Dumping syndrome symptoms has "early" and "late" patterns. Early dumping begins within 30 min after a meal and may include abdominal pain/cramps, diarrhea, borborygmi, nausea, and bloating, as well as vasomotor symptoms of fatigue, flushing, palpitations, tachycardia, hypotension, lightheadedness, sweating, and syncope. Early dumping is attributable to bowel distension, gastrointestinal hormone secretion, and autonomic dysfunction [122]. Late dumping occurs 1–3 h after a meal and consists of a reactive hypoglycemia and vasomotor symptoms (including sweating, confusion, palpitations, fatigue) rather than predominant GI symptoms. Symptoms may be severe and disabling and can result in malnutrition and avoidance of eating. The two patterns of symptoms can coexist in the same patient. Many of these symptoms, particularly GI symptoms of early dumping, are also present in patients with gastroparesis, and many dumping syndrome patients may be first diagnosed with gastroparesis.

Dumping syndrome can be distinguished from gastroparesis by radionuclide scintigraphy and clinical presentation. Rapid gastric emptying with a standardized meal typically finds <35 % gastric retention at 1 h in early dumping syndrome and <20 % at 2 h in late dumping syndrome, although variable normative values are used. Clinical presentation remains key to diagnosis, with exclusively postprandial symptoms and the lack of history suggestive of other diseases (including carcinoid syndrome, pancreatic insufficiency, or other causes of hypoglycemic episodes). Sigstad's clinical scoring system can be utilized in adults with graded rating of symptoms [123] to aid in distinguishing from other disorders and to follow symptom course/response to therapy. The oral glucose challenge is a provocative test that can also assist in diagnosis of dumping syndrome. After a 10-h fast, 50 g glucose is ingested. Heart rate (HR) and blood pressure before, during, and 3 h after ingestion are recorded. An increase in HR >10BPM after 30 min is indicative of dumping syndrome [124]. Associated tests of hematocrit (increase greater than 3 % in first 30 min) and serum glucose (hypoglycemia 2–3 h after ingestion) can also be performed. In adults, the oral glucose challenge has sensitivity of 100 % and specificity of 94 %. All tests listed above are limited by lack of validation in pediatric patients, but continue to serve as useful clinical tools [124].

Treatment of dumping syndrome is typically through dietary modification. To prevent symptoms, the portion size is reduced, and frequent small meals composed of few monosaccharides and high fiber are recommended. Other dietary strategies include increasing viscosity of food with addition of uncooked cornstarch, guar gum, or pectin [125–127]. Continuous enteral feeding can be considered when initial dietary strategies are ineffective. Acarbose is an alpha-glucosidase inhibitor useful for treatment of late dumping syndrome [128]. It competitively inhibits brush-border enzymes, delaying glucose and fructose absorption and preventing significant postprandial hypoglycemia. Acarbose was shown to be effective in adults with T2DM-associated late dumping syndrome [129], as well as children with late dumping who are refractory to dietary management [130, 131]. Potential adverse effects of acarbose include diarrhea and bloating.

Octreotide has been reported to be beneficial in a systematic review of dumping syndrome patients refractory to dietary management [132]. Octreotide slows gastric emptying, inhibits

insulin release, decreases enteric peptide secretion, increases intestinal absorption of water and sodium, and prevents hemodynamic changes, thereby alleviating dumping syndrome symptoms. Octreotide is typically given by subcutaneous injection three times daily, although long-acting (depot) octreotide also is effective [133, 134].

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The term pseudo-obstruction literally denotes obstruction in the absence of true mechanical occlusion. Intestinal pseudo-obstruction can be either acute or chronic in nature depending on the duration of obstructive symptoms (chronicity defined as symptoms' duration longer than 6 months) [1, 2]. Chronic intestinal pseudo-obstruction (CIPO) was first described in 1958 by Dudley and colleagues to report a series of 13 patients with symptoms suggestive of intestinal occlusion. These patients underwent exploratory laparotomies, which failed to identify a mechanical cause [3]. The existence of this pathological entity, in both the adult and pediatric population, was later substantiated by a number of other clinicians [4–7].

Abnormal antegrade propulsive activity of the gastrointestinal (GI) tract, resulting from processes affecting its neurons, muscles, or interstitial cells of Cajal (ICC), is the pathophysiologic mechanism of CIPO [8]. This functional disability of the gut is responsible for a number of clinical symptoms such as abdominal distention, with or without abdominal pain, nausea, vomiting, and a reduced ability to tolerate oral and/or enteral nutrition [9]. Such symptomatology is, however, non-specific, and the condition can remain undiagnosed for a long period of time during which patients may undergo multiple diagnostic investigations and often repeated surgical explorations in an effort to identify the underlying cause [9].

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Although by definition the small intestine is always involved, any part of the GI tract can be affected in CIPO [1, 2]. Esophageal involvement may lead to dysphagia due to impaired peristalsis, in some cases similar to that seen in achalasia [10]. Involvement of the stomach results in poor feed tolerance due to gastroparesis suggested by the presence of delayed gastric emptying, while involvement of the large bowel and anorectum manifests with constipation (delayed colonic transit) and defecation disorders (sphincteric dysfunction), respectively [1].

This chapter will focus on various aspects of pediatric CIPO and will attempt to address areas of controversy by exploring the most recent advances in the overall approach and management of this clinical entity.

Definition

According to an ESPGHAN/international expert consensus paper on the disorder, CIPO in children has clear distinctions from CIPO in adults with the proposal it be designated pediatric intestinal pseudo-obstruction (PIPO) rather than CIPO and be defined as follows: "Paediatric intestinal pseudo-obstruction is a disorder characterised by the *chronic inability of the gastrointestinal tract to propel its contents mimicking mechanical obstruction, in the absence of any lesion occluding the gut" (*chronic is defined as persistence for 2 months from birth or at least 6 months thereafter). The working group has suggested that the diagnosis of PIPO requires at least two out of four of the following criteria:

1. Objective measure of small intestinal neuromuscular involvement (abnormal validated transit, manometric, and/or histopathology studies)
2. Recurrent and/or persistently dilated loops of small intestine with air-fluid levels
3. Genetic, metabolic, or other abnormalities definitively associated with intestinal pseudo-obstruction

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4. Inability to maintain adequate nutrition and/or growth on normal oral feeding (therefore needing specialized oral and/or enteral nutrition and/or parenteral nutrition support)

For the purposes of this chapter, no distinction will be made between PIPO and CIPO, and the latter will be used to designate chronic intestinal pseudo-obstruction in children.

Epidemiology

CIPO is a rare disease; scanty epidemiological data exist regarding its incidence and prevalence in both adult and pediatric populations. A survey-based study estimated that approximately 100 infants are born in the USA every year with CIPO, suggesting an incidence of approximately 1 per 40,000 live births [11, 12]. A recent nationwide survey for pediatric CIPO performed in Japan revealed that among children younger than 15 years of age, the prevalence of CIPO was 3.7 in one million children, of whom 56.5% developed CIPO in the neonatal period [13]. In another nationwide Japanese survey, 138 cases of CIPO were identified, with an estimated prevalence of 1.0 and 0.8 cases, and incidence of 0.21 and 0.24 cases, per 100,000 males and females, respectively [14]. Adult studies reveal that the disease is more frequent in females [15–17]. Undoubtedly the development of national registries is of paramount importance to delineate the precise epidemiologic characteristics of this orphan disease.

Classification

The classification of CIPO is still challenging. Conditions resulting in CIPO can be classified by whether they primarily affect intestinal nerves (neuropathy), smooth muscle (myopathy), or interstitial cells of Cajal (ICC) (mesenchymopathy). The abovementioned conditions can be further subdivided into primary or secondary, congenital or acquired, and diffuse or segmental depending on the mode of inheritance, presentation, likely etiopathogenesis, or what part of the GI tract is involved. Where classification is not possible, they are defined as idiopathic. In truth, there is a considerable overlap [1, 2].

In primary CIPO the disease is usually localized to the gastrointestinal tract, whereas in secondary cases there is a systemic disorder that directly or indirectly affects GI tract motility. Notably, in some cases of primary CIPO, extragastrointestinal involvement may also be part of the clinical picture; examples include disorders of the urinary tract (e.g., hollow visceral myopathy and megacystis-microcolon-intestinal hypoperistalsis syndrome), the nervous system (e.g., central, peripheral, or autonomic neuropathies), and/or mitochondria [e.g., mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)] [2, 18, 19]. Approximately 50% of CIPO cases qualify as secondary CIPO as presented in Table 24.1 (this is particularly true for adult CIPO patients, whereas in pediatrics the disease is predominantly idiopathic or due to primary causes) [20]. Based on histological findings, both primary and secondary CIPO can be further categorized into neuropathies, myopathies, and mesenchymopathies [21–26]. Although the onset of the disease is used to label whether CIPO is congenital or acquired, in children this area needs further elucidation [2, 8, 27].

Table 24.1 Classification of chronic intestinal pseudo-obstruction

Primary CIPO
• Sporadic or familial forms of hollow visceral myopathy/neuropathy (e.g., megacystis-microcolon-intestinal hypoperistalsis syndrome) [7, 28–45]
• Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) [19, 46–48]
• Hirschsprung disease [49–51]
• Neuropathy associated with multiple endocrine neoplasia type IIB [52–54]
• Malrotation or gastroschisis [55–57]
• Neuropathy post-neonatal necrotizing enterocolitis [58]
Secondary CIPO
• Conditions affecting GI smooth muscle
– Rheumatological conditions (dermatomyositis/polymyositis, scleroderma, systematic lupus erythematosus, Ehlers-Danlos syndrome) [59–70]
– Other (Duchenne muscular dystrophy, myotonic dystrophy, amyloidosis, ceroidosis or alternatively reported as brown bowel syndrome) [71–80]
• Pathologies affecting the enteric nervous system (familial dysautonomia, primary dysfunction of the autonomic nervous system, neurofibromatosis, diabetic neuropathy, fetal alcohol syndrome, post-viral-related CIPO, e.g., CMV, EBV, VZV, JC virus) [81–96]
• Endocrinological disorders (hypothyroidism, diabetes, hypoparathyroidism, pheochromocytoma) [97–101]
• Metabolic conditions (uremia, porphyria, electrolyte imbalances, e.g., potassium, magnesium, calcium) [102–107]
• Other (celiac disease, eosinophilic gastroenteritis, Crohn's disease, radiation injury, Chagas disease, Kawasaki disease, angioedema, mitochondrial disorders, drugs, e.g., opiates, anthraquinone laxatives, calcium channel blockers, antidepressants, antineoplastic agents, e.g., vinca alkaloids, paraneoplastic CIPO, major trauma/surgery, chromosome abnormalities) [108–134]
Idiopathic

Etiology and Pathophysiology

The integrity of gastrointestinal sensorimotor function relies on a precise coordination between the autonomic nervous system, ENS, ICC, and smooth muscle cells. Any noxious stimulus, as depicted in Table 24.1, which affects the GI neuromusculature may lead to impaired peristalsis and the stasis

of luminal contents (1). Neurologic and metabolic disorders may affect the extrinsic GI neurons, whereas neurotropic viruses could evoke an inflammatory process insulting both the ENS and extrinsic nerve pathways [20, 94]. Paraneoplastic syndromes could also target the ENS by initiating an inflammatory process that affects the ganglia of the submucosal and myenteric plexuses via a cellular infiltrate and production of circulating anti-neuronal antibodies [20, 135]. Some pathologies (e.g., muscular dystrophy) target the enteric smooth muscle fibers, whereas entities such as dermatomyositis, scleroderma, Ehlers-Danlos syndrome, and radiation enteritis lead to a mixed neuro-myopathic disorder [12, 136, 137]. Celiac disease, hypothyroidism, hypoparathyroidism, and pheochromocytoma could also lead to CIPO by affecting the GI neuromusculature; however, the exact mechanism is not fully defined.

Genetics

Elucidation of the genetic basis of CIPO has been somewhat disappointing. Some familial cases of CIPO have been recognized, but there appear to be several patterns of inheritance, perhaps reflective of the great heterogeneity of CIPO conditions. Both autosomal dominant and recessive modes of inheritance have been described for neuropathic and myopathic types of CIPO [5, 15, 16, 136, 138]; nonetheless, the majority of CIPO cases are sporadic with no defined or recognizable genetic background.

Genes involved in congenital aganglionosis (i.e., Hirschsprung disease) such as *GDNF* (glial-cell-derived neurotrophic factor), one of its related receptors (*GFRA1*, GDNF receptor-alpha-1), *EDN3* (endothelin 3), and its related receptor (*EDNRB*, endothelin 3 receptor B) have not, as yet, been shown to play a role in CIPO. On the other hand, three patients with a syndromic phenotype of CIPO combined with Waardenburg-Shah features (pigmentary abnormalities and sensorineural deafness) and an underlying "apparently normal" enteric innervation have been demonstrated to carry de novo heterozygous mutations of *SOX10* [139, 140]. Additionally, mutations in the following genes, *filamin A* [141], *actin γ-2* [43], *thymidine phosphorylase (TYMP)* [142], polymerase γ (*POLG1*) [143], and, finally, *RAD21* [144] and *SGOL1* [145], have also been identified in recessive forms of CIPO with an associated syndromic phenotype (Fig. 24.1). Affected families may benefit from genetic counseling.

Specific genetic mutations are associated to complications. Medullary thyroid carcinoma associated with MEN2b and neurogangliomatosis should be searched for by measuring serum calcitonin levels, and early prophylactic thyroidectomy may be considered [146]. In cases with cardiac involvement (SGOL1), a pacemaker is indicated since severe bradycardia may occur [145]. Filamin A gene on chromosome X as well as thymidine phosphorylase mutations are both associated to seizures and impaired neurological development [141].

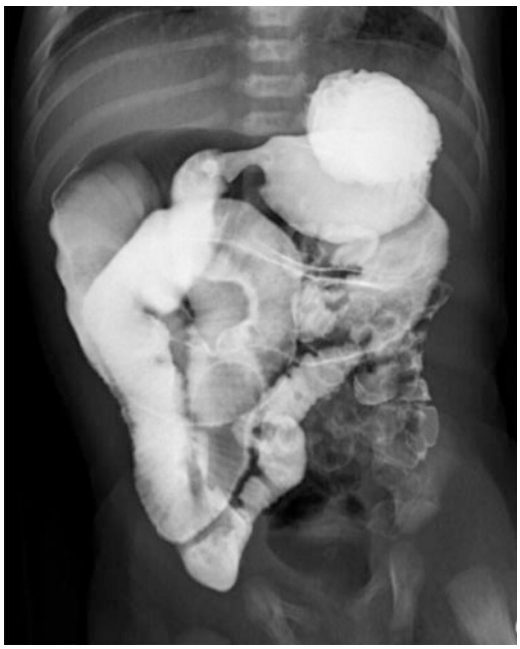

Fig. 24.1 Small bowel follow-through in a 6-month-old boy with an X-linked filamin A mutation-related CIPO. Note the malrotation, narrowed pylorus, and enlarged bowel loops

Histopathology

Studies in adults with CIPO reveal that GI histology can be normal in up to 10% of cases, although in the experience of the authors, this figure is likely to be higher in children. The role of histopathology in the diagnosis of CIPO is crucial; adequate full-thickness bowel biopsy (preferably a circumferential sleeve of at least 1–2 cm) is recommended whenever surgery is being considered [8, 27, 147]. Recent initiatives support a more standardized histological approach for the diagnosis in GI dysmotilities such as CIPO [26, 148, 149] (See Chap. 17).

On the basis of histology, CIPO is classified into neuropathy, myopathy, or mesenchymopathy; mixed forms (e.g., neuromyopathy) are also recognized [26, 150–152].

Neuropathies and myopathies can be further subdivided into inflammatory and degenerative. Inflammatory neuropathies are characterized by an infiltration of T lymphocytes and plasma cells in the myenteric plexuses (myenteric ganglionitis) and neuronal axons (axonopathy); five or more lymphocytes per ganglion are required for the diagnosis of myenteric ganglionitis [26, 153]. Interestingly, patients with lymphocytic infiltration of the myenteric plexus may also develop increased titers of antinuclear antibodies (ANNA-1/anti-Hu, anti-VGKC); the

latter could result in neuronal degeneration and loss via apoptotic and autophagic mechanisms [154–157]. Infiltration of the myenteric ganglia with other cells such as eosinophils and mast cells has also been identified, but their clinicopathological significance is yet to be determined [158–161].

Degenerative neuropathies are defined by a decrease in the number of intramural neurons along with changes in nerve cell bodies and axons [148, 153, 162–164]. It has been postulated that aberrant calcium signaling, mitochondrial disorders, production of free radicals, and abnormalities in the function of glial cells initiate apoptotic mechanisms that are involved in the degenerative process [148, 150, 165, 166].

Myopathies are also categorized as inflammatory and degenerative. Inflammatory myopathy, also termed leiomyositis, is characterized by infiltration of T lymphocytes into both the circular and longitudinal enteric muscle layers and if not treated appropriately with immunosuppressive agents may lead to a severe clinical picture of CIPO [45, 167]. A distinctive presumably acquired degenerative myopathy of unknown etiology, called African degenerative leiomyopathy (ADL), has been described in African populations in southern Africa [168]. The RET gene implicated in Hirschsprung disease appears to confer susceptibility to ADL although the exact mechanism is not known [169].

Histopathology in degenerative myopathies reveals vacuolization and fibrosis of the smooth muscle fibers [170, 171]. In the cases where the longitudinal muscle is more affected compared to the circular muscle layer, diverticula may be identified [172, 173].

Novel techniques in immunohistochemistry, e.g., smooth muscle markers such as smoothelin, smooth muscle myosin heavy chain, and histone deacetylase 8, may reveal subtle histopathologic abnormalities otherwise not detectable with conventional methods [174].

Mesenchymopathies are defined by ICC abnormalities (decreased density of ICC network, intracellular abnormalities) and have been identified in CIPO patients [148, 175]. Despite the fact that adequate data exist regarding the role of ICC in the pathogenesis of diabetic gastroparesis, further research is required to elucidate their involvement in the pathogenesis of other GI dysmotilities [26].

Clinical Picture

Signs and Symptoms

The symptomatology varies according to the age at diagnosis and the part of the GI tract, which is primarily affected. Intestinal malrotation is present in approximately one third of children with congenital CIPO (myopathic and neuropathic) [23]. Cardinal signs and symptoms of CIPO include those of obstruction, namely, abdominal distention (88 %), vomiting (69 %, which can be bilious), and constipation (54 %). Abdominal pain, failure to thrive, and diarrhea may also be part of the clinical picture (Table 24.2, Fig. 24.2) [8, 9, 147].

The diagnosis of CIPO is difficult due to the variable clinical presentation and the lack of a specific diagnostic test. The diagnosis should be suspected in children presenting with signs and symptoms of intestinal obstruction without an occluding lesion. The diagnosis of CIPO should be also considered when there is persistent vomiting after a Ladd's procedure for malrotation [56] when intestinal obstruction is associated with bladder dysmotility or when, in a full-term neonate, there is persistent or recurrent obstruction after exclusion of Hirschsprung disease and hypothyroidism. The differential diagnosis should be carefully considered because establishing a diagnosis of CIPO may be invasive, and the

Table 24.2 Clinical symptoms in children with chronic intestinal pseudo-obstruction

Study	Abdominal distension	Vomiting	Constipation	Failure to thrive	Abdominal pain	Diarrhea	Dysphagia
Faure et al. [176]	100	94	70	64	46	29	9
$n=105$							
Vargas et al. [11]	73	50	51	23	NA	21	2
$n=87$							
Granata et al. [177]	59	31	27	NA	NA	26	NA
$n=59$							
Schuffler et al. [29, 197]	23	19	20	15	NA	16	NA
$n=30$							
Heneyke et al. [22]	31	40	31	NA	NA	–	NA
$n=44$							
Muto et al. [13]	55	33	9	NA	3	2	NA
$n=62$							
Total	341 (88 %)	267 (69 %)	208 (54 %)	102 (31 %)	–	94 (24 %)	11 (3 %)
$n=387$							

NA, not available

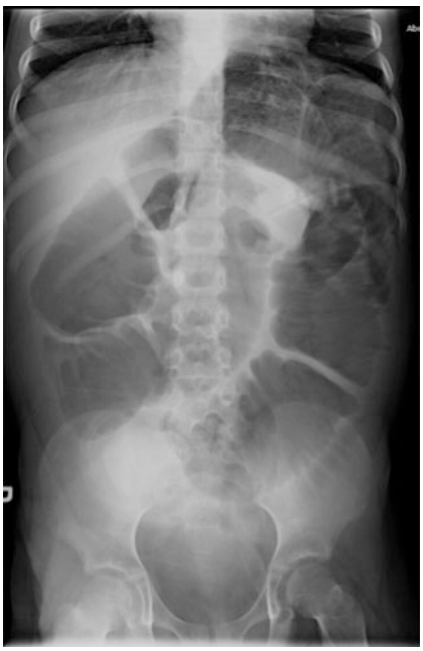

Fig. 24.2 Plain abdominal X-ray in a 7-year-old girl with CIPO. Note the enlarged and hugely dilated small bowel loops

psychological consequences in children and their families are significant.

Dehydration (which can be severe) and malnutrition are often underdiagnosed especially given that weight can be an unreliable measure due to pooling of significant volumes of fluid (third spacing) within distended gut loops. Delayed transit of gut content can also lead to small bowel bacterial overgrowth which can further exacerbate symptoms of diarrhea and abdominal distention [147].

Extraintestinal signs and symptoms may as well be part of the CIPO clinical presentation, e.g., recurrent urinary tract infections or neurologic abnormalities [18, 142]. Furthermore, patients may complain of symptoms indicative of an underlying disorder that accounts for secondary CIPO (e.g., proximal muscle weakness in dermatomyositis) [60].

The clinical course of CIPO is characterized by exacerbations and remissions; the former can be precipitated by various factors such as surgery, general anesthesia, infections, and emotional stress [27]. In the most severe cases, the natural course of the disease leads to significant deterioration of the intestinal function and ultimately in intestinal failure [9, 147].

Prenatal Symptoms

Although the majority of CIPO cases present in the neonatal period or early infancy, in a few cases the diagnosis is supported in utero by ultrasonographic findings of polyhydramnios, abdominal distention, and megacystis [8, 27]. Prenatal signs can be detected in about 20 % of cases [22, 176]. Megacystis is the most frequently reported sign, whereas dilated bowel at this age is quite rare. This has been noted in megacystis-microcolon-intestinal hypoperistalsis syndrome in which an antenatally enlarged bladder is seen by ultrasound in 88 % of cases, hydronephrosis in 53 %, increased volume of amniotic fluid in 34 %, and gastric distension in only 10 % [177]. Although some reports have described the detection of these signs by ultrasound as early as 16 weeks, more often the abnormalities are noted much later in gestation [178]. Antenatally diagnosed non-obstructive megacystis, with neonatal urological symptoms, may precede GI symptoms of pseudo-obstruction by several months.

Clinical Presentation After Birth

Fifty percent to two thirds of patients present within the first month of life and 80 % by 1 year of age. The remainder are detected sporadically throughout the first two decades of life [11, 21, 22, 176]. The clinical presentation is dependent on the age at onset.

Neonatal-Onset Form

In the neonatal form, CIPO presents as severe abdominal distension with bilious vomiting. Although not a universal finding, the abdominal X-ray may show dilated bowel loops with air-fluid levels suggestive of an organic intestinal obstruction. In megacystis-intestinal-hypoperistalsis syndrome, an obstructed urinary system leading to an abdominal distension may be the presenting feature, with symptoms of intestinal obstruction appearing within days to 12 months later. In order to avoid unnecessary surgery, an exploratory laparotomy should be deferred in a neonate with antenatal diagnosis of megacystis. In these neonatal cases, the air-fluid levels on X-ray may be missing. Some affected infants may present with abdominal distension and diarrhea secondary to bacterial overgrowth.

CIPO may be mimicked by immaturity of intestinal motility in preterm infants, and, thus, this diagnosis should be made with caution in this group as the migrating motor complex does not appear in its mature form until a gestational age of 34–35 weeks [179, 180].

Infantile or Late-Onset Form

The symptoms depend on the regions of the gastrointestinal tract primarily involved. Patients present with subacute and/or recurrent episodes of gastric, intestinal, and/or colonic obstruction necessitating frequent drainage and fluid replacement. This picture may be acute or insidious and chronic and persistent or more often intermittent. Exacerbations may be precipitated by a variety of causes including intercurrent infections, fever, vaccines, general anesthesia, and emotional stress. Diarrhea due to bacterial overgrowth is frequent and

may alternate with constipation or episodes of partial obstruction. Stasis of intestinal contents is common in CIPO, and chronic dilatation leads to decompensation and elongation of the bowel, further impairing motility. When fluid and air accumulate in these decompensated loops, torsion caused by mechanical forces is possible. Dehydration (which can be severe) and malnutrition are often underdiagnosed especially given that weight can be an unreliable measure due to pooling of significant volumes of fluid (third spacing) within distended gut loops (147). Mechanical obstruction is normally absent in CIPO patients, but it can however be a complication of CIPO, especially after multiple interventions. Volvulus of the splenic flexure and colonic volvulus have been reported in numerous CIPO cases due to torsion of fluid-filled bowel loops [181–183].

Abdominal pain is often severe enough to lead to feeding difficulties resulting in malnutrition. Notwithstanding frequently detected esophageal involvement by manometry, dysphagia is rarely reported [184]. Recurrent episodes of functional partial bowel obstruction may be very difficult to differentiate from true mechanical obstruction in the child who has undergone a prior laparotomy and who may have adhesions. A change of symptoms such as the new occurrence of abdominal pain may suggest the latter.

Urinary tract involvement occurs in 33–92 % of cases, independent of the type of CIPO [176, 185–187]. Megacystis with a hypo-contractile detrusor, increased bladder capacity, and compliance is the most frequent pattern of urological abnormality (bladder adynamia). Ureterohydronephrosis is seen in 56–68 % of cases, but vesicoureteral reflux occurs in less than 10 % [187]. Urinary tract infections are frequent but may be asymptomatic. The renal prognosis is generally good, provided that careful, active evaluation and management of the poorly dynamic bladder are performed to ensure adequate bladder emptying and to prevent urinary tract infection [187]. Where they are taken, bladder biopsies show nonspecific fibrotic changes in both neuropathic and myopathic forms of CIPO and are thus not useful for subtype classification.

Comorbidities

Malrotation is frequent, especially in neonates (up to 40 % of cases) [21, 22, 176], and has been reported in X-linked familial syndromes associating CIPO, malrotation, and pyloric non-hypertrophic stenosis [141, 188–190] (Fig. 24.1).

The physical examination should encompass a thorough neuromuscular assessment, including testing for pupillary reactions to light and accommodation and external ocular movements to help identify conditions associated with autonomic neuropathy or mitochondrial diseases. Testing for orthostatic stability should be performed in children, especially where postural dizziness, visual disturbances, and sweating abnormalities may suggest the presence of an underlying autonomic neuropathy [41].

External ophthalmoplegia associated with deafness may suggest a mitochondrial defect, namely, mitochondrial neurogastrointestinal encephalopathy (MNGIE). The onset of symptoms (gastrointestinal or ocular or both) generally occurs during adolescence, although very early-onset disease has been reported (5 months of age) [191]. Peripheral neuropathy and diffuse muscle weakness are the predominant manifestations, although almost all patients have indices of leukoencephalopathy on magnetic resonance imaging of the brain [48]. Thymidine phosphorylase activity and plasma thymidine should be measured when suspecting such a diagnosis [192]. Audiological assessment is important to rule out deafness, seen in patients with a *SOX10* gene mutation [139, 140]. The dermatological examination should note signs of connective tissue disease (i.e., scleroderma, dermatomyositis, lupus) including: Raynaud's phenomenon, skin eruption, palmar erythema, telangiectasia, nodules, and scleroderma of the hands, feet, face, and forearms. Digestive symptoms may precede the skin involvement in these disorders [193].

Neural crest-derived tumors and pheochromocytoma should be suspected and ruled out in children and infants with CIPO; appropriate CT imaging and ultrasound studies should be considered to exclude the presence of thoracic or abdominal tumors [194].

Cardiac rhythm and function must be evaluated by ECG and echocardiography, since dysfunction of the cardiac sinus node may be associated to CIPO [195], and abnormal cardiac contraction should lead one to suspect muscular diseases such as desmin myopathies [196].

Diagnosis

Chronic intestinal pseudo-obstruction should be suspected in children with early-onset, chronic, recurrent, or continuous signs of intestinal obstruction especially where imaging or indeed surgery fails to reveal a mechanical obstruction of the gut (e.g., repeated "normal" exploratory laparotomies). Since the symptoms of CIPO are not specific, a careful differential diagnosis is of paramount importance.

The diagnosis of CIPO should be guided by a structured algorithm. A detailed history combined with a meticulous clinical examination and laboratory tests (e.g., serum electrolytes, TSH, lactic acid, specific autoantibodies) may suggest the presence of CIPO and potentially elucidate its cause; however, the establishment of a definitive diagnosis should rely on the use of targeted investigations to (1) exclude mechanical occlusion of the gut lumen, (2) confirm GI dysmotility, and (3) rule out treatable causes.

The diagnostic tests, which exclude luminal obstruction and confirm the presence of impaired GI motility in children, thus ruling in the diagnosis of CIPO, are discussed below.

Imaging

Since small bowel is always involved, plain abdominal radiographs demonstrate a dilated GI tract, with air-fluid levels (Fig. 24.2), while contrast GI series can demonstrate anatomical abnormalities (e.g., malrotation, microcolon) and also exclude the presence of gut occlusive lesions [2, 147, 197, 198] (Fig. 24.3 & 24.4). It needs to be kept in mind that a water-soluble substance should be used instead of barium in order to prevent flocculation and inspissation of the contrast material.

Novel imaging modalities such as multidetector row helical CT and cine-MRI have been recently performed with promising results in adult series, but there is currently limited data regarding their applicability and usefulness in pediatrics [199–201].

Endoscopy

Endoscopy may identify upper or lower bowel mechanical occlusion previously missed on radiology and allows for duodenal biopsies to exclude mucosal inflammation [195]. Novel techniques (e.g., natural orifice transluminal endoscopic surgery—NOTES) may revolutionize the role of endoscopy in the diagnosis of gut motility disorders by providing the ability of full-thickness biopsy sampling in a safe and minimally invasive way [202, 203].

Motility Investigations

These studies are performed in order to assess the GI motility and to define the underlying pathophysiologic process; in pediatrics they form the hallmark of diagnosis. The aforementioned studies include gastrointestinal manometries (esophageal, antroduodenal, colonic, anorectal) (see Chaps. 7, 8, 9, and 10), scintigraphy (e.g., gastric emptying, colonic transit) (see Chap. 14), electrogastrography, and radiopaque marker studies (see Chap. 15). The usefulness of novel technologies, such as SmartPill, remains to be determined [8, 204, 205].

Although in children with CIPO the involvement of the GI tract may be generalized, the small intestine is always affected; thus, antroduodenal manometry remains the most discerning test. It needs to be stressed, though, that the optimal placement of the manometric catheter is of pivotal significance for a *lege artis* execution and precise interpretation of this test [206]. Neuropathic cases manifest with uncoordinated contractions, which are of normal amplitude, whereas in myopathic CIPO motor patterns have normal coordination; however, the amplitude of intestinal contractions is low [184, 207, 208]. Additionally, manometry may facilitate the dynamic assessment of potential pharmacotherapeutic options and feeding strategies (e.g., feasibility of oral or enteral feeds) as well as indicate disease prognosis [209–211]. Antroduodenal manometry features suggestive of CIPO are depicted in Table 24.3 and also described in Chap. 8.

In the most challenging cases, exploratory surgery (laparotomy or laparoscopic-assisted procedures) may be required to definitively exclude mechanical obstruction; however, it should be borne in mind that surgery may precipitate a

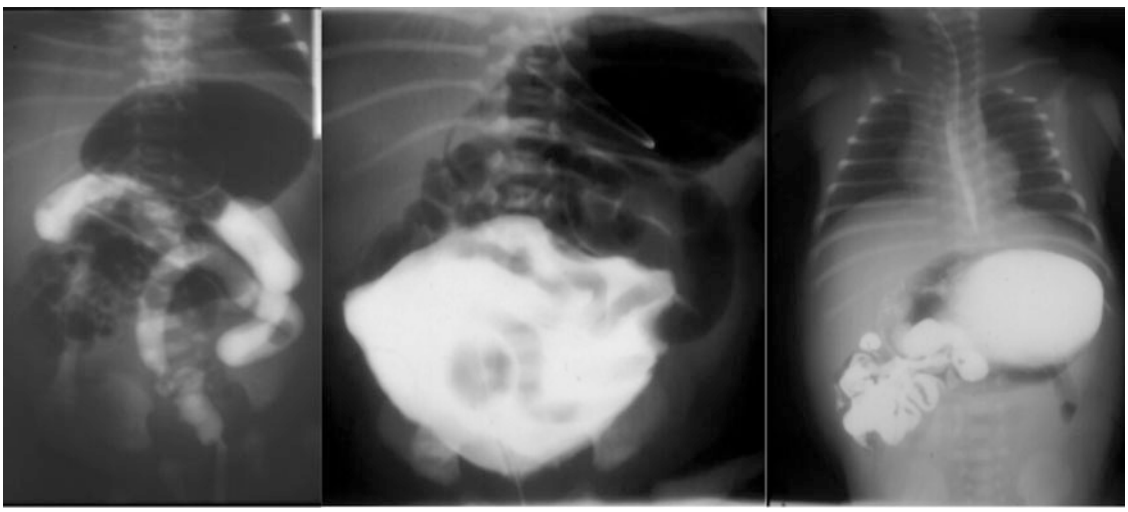

Fig. 24.3 Girl neonate with megacystis, microcolon, and hypoperistalsis syndrome. *Left*: Colonic opacification showing small nonfunctional microcolon. *Middle*: Cystography demonstrating enlarged bladder with "footprints" of digestive loops. *Right*: Small bowel follow-through showing malrotation and nonfunctional small bowel. In neonates, despite the small bowel involvement precluding any enteral feeding, the small bowel loops may not be enlarged converse to older children in whom dilated small bowel is always present

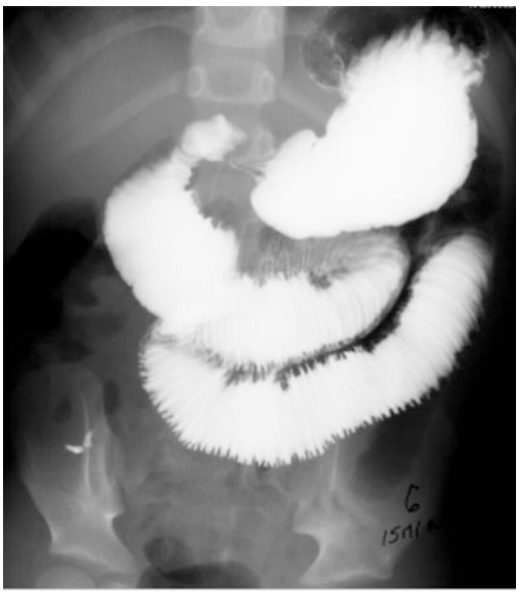

Fig. 24.4 Small bowel follow-through in a 6-year-old boy with CIPO. Note the enlarged and dilated small bowel loops

Table 24.3 Features in antroduodenal manometry associated with CIPO

Interdigestive or fasting period
Absence of phase III
Short intervals between phase III
Abnormal phase III
– Stationary
– Retrograde
Non-migrating burst of contractions[a]
Sustained simultaneous cluster of contractions[b]
Low-amplitude contractions
Postprandial or fed period
Failure to switch to postprandial period
Postprandial hypomotility
– Low frequency of contractions
– Low amplitude of contractions
Non-migrating cluster of contractions

[a]Burst of contractions is defined as sequences of intense irregular pressure waves not satisfying the definition for phase III of MMC
[b]Cluster of contractions is defined as the presence of three to ten pressure waves of slow frequency showing higher amplitude and duration than isolated individual contractions

pseudo-obstructive episode and may also lead to intra-abdominal adhesion formation, which in turn can further complicate future diagnostic or therapeutic procedures as well as lead to secondary mechanical obstruction. Where possible, investigations and then diagnostic/therapeutic surgery should be performed in timeline sequence and in referral centers with relevant expertise in the management of CIPO patients.

Histopathology along with genetics can also be very useful in establishing or confirming the diagnosis of CIPO, highlighting the underlying pathophysiologic process and thus aiding the overall management. Figure 24.5 summarizes the basic steps in the diagnostic evaluation of pediatric patients with suspected CIPO.

Differential Diagnosis

CIPO has to be differentiated from mechanical obstruction of the GI tract; the latter is usually characterized by marked abdominal pain (in keeping with the abdominal distention), specific radiologic signs, and manometric patterns [212, 213]. Acute functional obstruction (e.g., postoperative ileus), functional GI disorders (e.g., rumination syndrome), and pediatric condition falsification should be considered and appropriately investigated and managed [147, 214, 215]. Table 24.4 provides differential diagnoses of CIPO.

Treatment

The therapeutic approach in CIPO is threefold as it aims to (1) preserve growth and development by maintaining adequate nutritional intake; (2) preserve and even promote GI motility with combined medical and surgical interventions; and (3) treat disease-related complications or underlying pathologies in the cases of secondary CIPO.

In spite of the limited effect of the currently applied therapeutic options, refinements and evolution in nutritional, medical, and surgical strategies have considerably improved the overall CIPO management [137, 216]. Acute episodes of pseudo-obstruction are generally treated conservatively by intravenous fluid administration (patients remain nil by mouth) and decompression of the affected bowel with drainage of luminal contents via NG tube or preformed ostomies. Careful attention to fluid and electrolytes' balance is imperative.

Nutrition

The role of nutrition in CIPO is of paramount significance as it is well established that gut motility improves with optimal nutritional support and declines in the face of under- or malnutrition [8]. In the long term, approximately one third of pediatric CIPO patients require either partial or total parenteral nutrition; another third requires a degree of intragastric or enteral feeding, whereas the remaining children are able to tolerate sufficient oral nutrition. Within all of the abovementioned groups, patients able to tolerate feeds may require

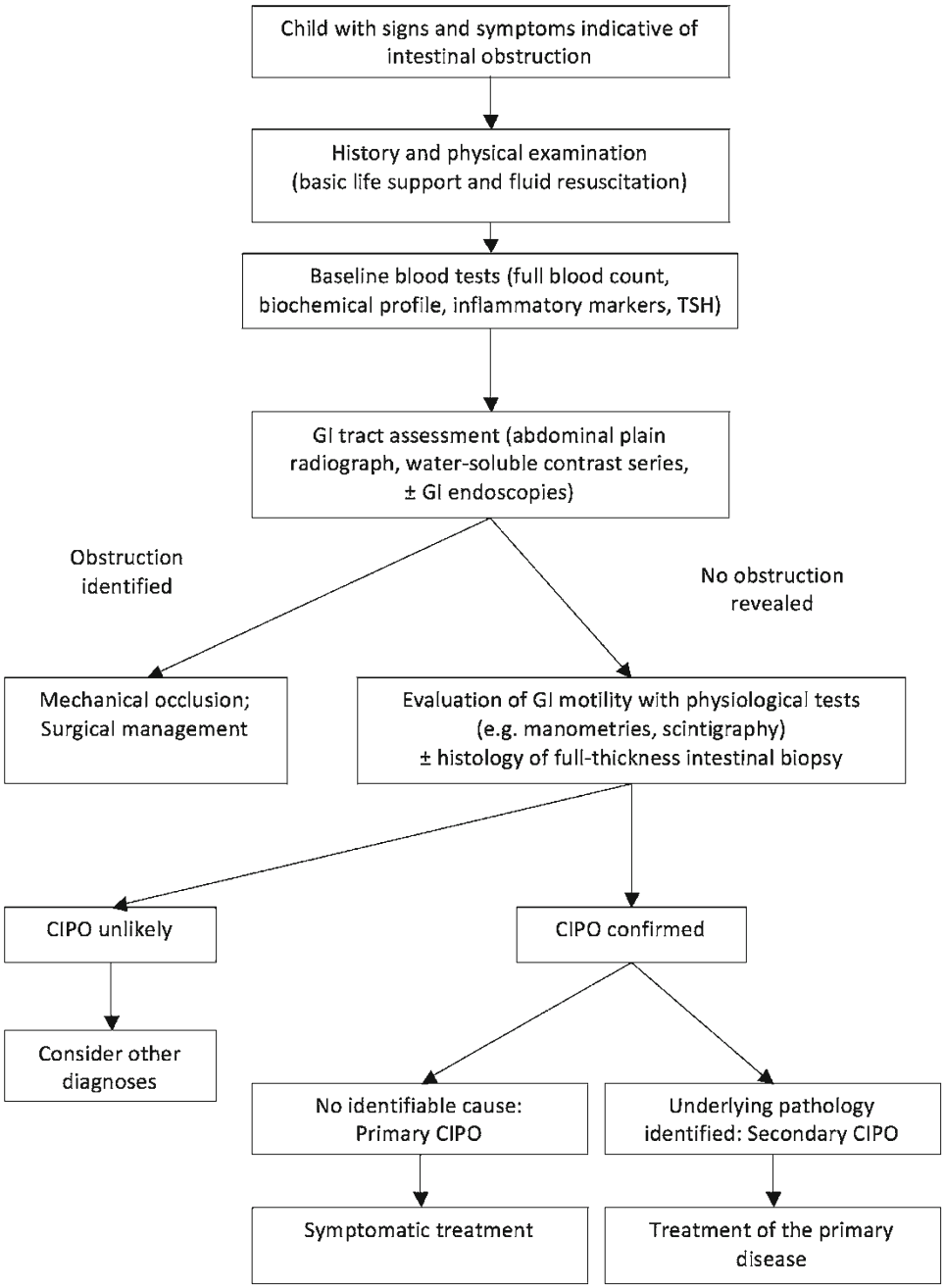

Fig. 24.5 Suggested diagnostic algorithm for childhood chronic intestinal pseudo-obstruction. (Modified from Rudolph CD, Hyman PE, Altschuler SM, Christensen J, Colletti RB, Cucchiara S, et al. Diagnosis and treatment of chronic intestinal pseudo-obstruction in children: report of consensus workshop. J Pediatr Gastroenterol Nutr. 1997;24(1):102–12, with permission)

Table 24.4 Differential diagnosis of CIPO in children

Aerophagia
Gastroparesis
Constipation
Rumination syndrome
Cyclic vomiting syndrome
Severe irritable bowel syndrome
Bacterial overgrowth of various origin (lactase deficiency, disaccharidase deficiency, intestinal duplication)
Aerodigestive fistula
Fabricated or induced illness (Munchausen's syndrome or pediatric falsification disorder)

some dietary modification in order to maintain enteral nutrition and avoid bezoar formation (e.g., low residue feeds, bite and dissolvable food, restriction diets, hydrolyzed formula).

Although parenteral nutrition is lifesaving, it is associated with significant risk of complications, such as central line infections and liver disease; thus, maintaining patients on maximally tolerated enteral nutrition is always strongly encouraged [27]. In the more severe CIPO cases, continuous rather than bolus feeds administered via a gastrostomy or jejunostomy may be better tolerated; the latter is particularly true in those children with impaired gastric motor function [217–219].

Medications

Pharmacotherapy in CIPO patients is mainly confined to the control of intestinal inflammation, suppression of bacterial overgrowth, and promotion of GI motility [210, 219]. In cases of a proven inflammatory process confirmed on full-thickness intestinal biopsies and histology such as lymphocytic or eosinophilic ganglionitis and inflammatory leiomyositis, immunosuppression may be needed.

Prokinetics (e.g., metoclopramide, domperidone, erythromycin, azithromycin, octreotide, neostigmine) and antiemetics (e.g., promethazine, ondansetron) have been used to reduce the severity of nausea and vomiting and improve the GI motor function [220–223]. The use of some of these agents is limited because of their variable efficacy and unacceptable extra-intestinal side effects (e.g., metoclopramide, neostigmine). The best studied and tested prokinetics, i.e., cisapride and tegaserod, have been withdrawn from the market due to safety concerns [224]. Recent data suggests that antibiotics such as co-amoxiclav may have prokinetic effects and induce an increased number of migrating motor complexes during the fasting phase of antroduodenal manometry. The need for novel prokinetics with increased safety profile and efficacy has resulted in the development of new products (e.g., prucalopride, aprepitant, ghrelin), but there is limited data of their use in pediatric CIPO, further impacted on by restricted availability and licensing [225–227]. Undoubtedly, current medical regimens for CIPO are based on limited literature and/or expert opinion (e.g., combined use of octreotide and erythromycin) and are yet to be tested in future in the context of controlled trials [210, 228].

Surgery

Surgery remains a valuable intervention on patients with CIPO as it has a multidimensional role in both the diagnostic (e.g., full-thickness biopsies) and therapeutic processes (e.g., insertion of feeding tubes, formation of decompressing ostomies such as gastrostomy, ileostomy) [219, 229, 230] (See Chap. 50).

Indeed, adequate bowel decompression (e.g., gastrostomy, ileostomy) is crucial not only in providing symptomatic relief by reducing the frequency and the severity of pseudo-obstructive episodes but also in limiting further deterioration of the intestinal motor activity secondary to chronic distention and in enhancing the tolerance of enteral feeding [21, 22, 219, 229, 231–233]. Long decompression enteral tubes and extensive bowel resections are approaches mainly reported in adult CIPO cohorts but remain untested in terms of practicality, efficacy, and safety in pediatrics [234–236]. Moreover, small bowel resections may lead to short gut syndrome and intestinal failure-associated liver disease [229, 237]. One additional concern is that resections of the small intestine may decrease the abdominal domain required for the successful outcome of a potentially necessary future intestinal transplantation [229, 237].

Other surgical procedures aiming in lengthening a dilated intestinal segment (e.g., longitudinal intestinal lengthening and tailoring, serial transverse enteroplasty) have shown promising results in children with intestinal failure including patients with CIPO [238].

Stoma prolapse [239], recurrent pancreatitis [240], diversion colitis [241], and excessive fluid losses with high ileostomy output [242] have been reported in patients with CIPO. In patients with gastric and upper digestive tract involvement, gastric perforation and gastric bezoars may occur [176].

Closure of the decompressive ileostomy and restoration of the gut continuity may be attempted in carefully selected patients who have demonstrated significant and clear improvement post-ileostomy formation, have managed to wean parenteral nutrition, and remain on full enteral and/or oral feeds without experiencing any troublesome symptoms for a period of at least 2 years. In the opinion of the authors, this is most likely to occur in neuropathic cases of CIPO and least in myopathies. In patients that show recovery with an ileostomy in situ, an ileo-rectal Duhamel pull-through has proven to be the most effective approach [22, 176, 236, 243].

The incidence of the enterostomy-associated complications is not insignificant in CIPO patients as these patients do have an increased rate of stomal prolapse along with a high risk of intestinal necrosis [239]. A meticulously constructed ileostomy combined with careful management of the ostomy reduces the probability of stomal prolapse, thus minimizing the risk of additional intestinal resection [22, 239].

Novel surgical methods involve implantation of devices providing electrical pacing of the GI neuromusculature, but data in children are scanty and limited [244]. Significant progress has been made in regenerative medicine especially with neural cell replacement within the bowel. This has not yet reached clinical trials and is hampered by poor disease characterization [245].

Small bowel transplantation still remains today the only definitive cure for CIPO. The outcomes and survival rates in experienced centers have significantly improved (up to 50 % survival rate at 3 years) during the last decade owing to advances in both the surgical approach (e.g., multivisceral transplantation) and the immunosuppressive treatment [238, 246–252] (see Chap. 50).

Natural History, Outcome, and Prognosis

Both pediatric and adult CIPO patients have a severe clinical course, characterized by repetitive relapses and remissions. Regrettably, the low index of suspicion among physicians, along with the lack of well-defined diagnostic criteria and

readily available facilities in performing specialized diagnostic tests (e.g., manometry), often accounts for repetitive unnecessary investigations and surgery as well as delayed diagnosis and thus initiation of appropriate management [15–17, 162].

The majority of the patients complain of symptoms, which progressively worsen and impact upon the tolerance of enteral nutrition consequently increasing reliance on total parenteral nutrition. The latter in conjunction with disease-related adverse events (e.g., central line infections, impairment of the liver function, immunosuppression after small bowel transplantation, surgical procedures) account for high morbidity, poor quality of life, and mortality rates up to 30 % [11, 22, 29, 176, 177, 197, 253, 254].

Despite recent diagnostic and therapeutic advances, CIPO in children remains a serious, life-threatening disease with significant impact on the well-being not only of patients themselves but of their families as well [254].

Outcome

In secondary and acquired forms of CIP, outcome is dependent of the underlying disease responsible for the dysmotility. In cases of destruction of enteric innervation or musculature, deterioration may occur rapidly without specific treatment [255].

Most often viral infection resolves spontaneously [83, 256] but some chronic cases have been reported [257, 258].

In primary forms of CIPO, the prognosis is poor. In one series of 105 patients, two thirds required parenteral nutrition and 41 % could not be enterally fed. More than half of the patients were TPN dependent for periods ranging from 2 months up to 16 years. Eleven patients (10 %) received TPN for more than 10 years. Twenty-four of the 58 patients who underwent bypass surgery were able to eat normally, and 20 of those eventually had their stoma closed [176]. Heneyke and colleagues reported that if TPN is required for more than 6 months, the child will probably be TPN dependent for at least 4 years [22].

Mortality

Progress in the management of parenteral nutrition and the use of bowel decompression have modified the high mortality rate reported in historical series in neonates, for whom up to 90 % of patients died before 1 year of age [57, 177]. In series published more recently, mortality varied from 4.8 % (3/62 patients) [13] to 10 % (10/105) [176] and 25 % (22/85) [21] and in one study just over 30 % (14/44) [22]. Of these, underlying CIPO is rarely the primary cause of death except in cases with MEN2B and medullary carcinoma. In pediatric series reported to date, the high mortality rate is almost always due to iatrogenic complications. Long-term TPN-related complications, including central venous catheter-associated sepsis, liver failure, and thromboembolic events, as well as posttransplantation complications are the major contributing factors to mortality and morbidity in CIP patients [21, 22, 176]. Sudden cardiac arrest has been reported in two patients with chronic intestinal pseudo-obstruction [259].

Prognostic Factors

In the large pediatric series published to date, comparison between patients requiring and those no longer requiring artificial feeding shows significant clinical differences in terms of likelihood of neonatal onset, urinary tract involvement, requirement for surgery during the course of the disease, and myopathic disorders, all features which are more frequent in cases with a poor prognosis [21, 22, 176]. The presence of phase III of the MMC on antroduodenal manometry has been reported by several groups to be a good prognostic indicator for tolerance of enteral feeding [184, 217] response to cisapride [209] and mortality [211]. Malrotation is also a factor associated with worse prognosis [22].

Summary

Pediatric CIPO is an enigmatic disease with poorly defined etiopathogenesis, which is reflected on the limitations encountered in both the diagnostic process and therapeutic management. Clearly multinational initiatives are required to raise awareness, establish stringent diagnostic criteria, and evolve current therapeutic modalities.

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Hirschsprung Disease

25

Robert O. Heuckeroth

There are many excellent articles on Hirschsprung disease (HSCR) that provide detailed information about the clinical presentation, epidemiology, genetics, diagnosis, and associated medical problems [1–7]. This chapter summarizes and simplifies the complex HSCR literature. Percentages in the text and tables are estimates, since widely divergent numbers are presented in different manuscripts.

Definition

The enteric nervous system (ENS) is an integrated network of neurons and glia that controls most aspects of intestinal function (see Chap. 2). This includes intestinal motility, response to luminal and intramural stimuli, regulation of epithelial activity, and control of blood flow [8, 9]. To perform these tasks, neurons are normally distributed along the entire length of the bowel. When the ENS is absent or defective in any region of the bowel, profound problems with intestinal function occur causing significant morbidity and in some cases death.

Hirschsprung disease, the most well-understood intestinal motility disorder, is characterized by the complete absence of enteric neurons (i.e., aganglionosis) in the myenteric and submucosal plexus of the distal bowel. In the absence of ganglion cells, the bowel tonically contracts causing functional intestinal obstruction. Many, but not all, clinical manifestations of HSCR result from tonic contraction of aganglionic bowel.

Nomenclature describing the extent of aganglionosis in HSCR is not consistent. However, most affected individuals have "short-segment" disease where aganglionosis is restricted to the rectosigmoid region of the colon [10, 11]. "Long-segment" HSCR aganglionosis extends proximal to the sigmoid colon and is usually distinguished from "total colonic" aganglionosis. In a small percentage of cases, aganglionosis extends into the small bowel leading to very serious lifelong disability often requiring total parenteral nutrition (Table 25.1) [11, 12]. Although some authors have suggested that clinical presentation varies with the length of aganglionosis [13], others say that clinical symptoms are not related to the extent of disease [14]. From a practical standpoint, it is best to assume that the extent of aganglionosis and the severity and character of symptoms are unrelated.

Clinical Presentation

HSCR is debilitating and can be fatal. Clinical presentation is highly variable and diagnosis requires a high index of suspicion. Recognizing HSCR is important since surgical management dramatically reduces disease morbidity and mortality.

In the current era, most people with HSCR are diagnosed by 6 months of age [15–18], but it remains common to diagnose HSCR in older children and HSCR has been diagnosed in adults up to 73 years of age [19]. HSCR needs to be considered in anyone with severe chronic constipation that began in early infancy, especially if suppositories or enemas are needed for stool passage. However, because constipation is common, affecting up to 35 % of all children [20, 21], and HSCR is rare (1/5000 people), recognizing distinct features that suggest HSCR is important for diagnosis. Furthermore, constipation is only one feature of HSCR. Typical presentations for HSCR include:

Neonatal Intestinal Obstruction

Infants present with marked abdominal distension and bilious emesis. Distension may be severe enough to cause respiratory compromise. Obstruction may occur on the first

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Table 25.1 Extent of aganglionosis

Short segment	74–89 %
Long segment	12–22 %
Total colon	4–13 %
Small bowel	3–5 %

day of life, but children may also initially have apparently normal bowel movements or "mild constipation" and then present acutely with abdominal distension and vomiting at an older age. Because HSCR requires a high index of suspicion for diagnosis, some infants are hospitalized repeatedly for episodes of presumed "gastroenteritis" that were actually a manifestation of HSCR-associated intestinal obstruction. The clinical distinction is that gastroenteritis may cause severe vomiting, but does not typically cause as much abdominal distension as HSCR. Vomiting associated with infectious enteritis is also usually followed by diarrhea, whereas intestinal obstruction should be accompanied by reduced stool passage. A distended abdomen occurs in 57–93 % of infants with Hirschsprung disease and bilious emesis occurs in 19–37 % [12, 14, 22–24]. Abdominal distension and bilious emesis are also a very common presentation in premature infants with HSCR (96 % and 92 %, respectively). Note that since the ENS forms during the first trimester of pregnancy, incidence of HSCR is similar in term and preterm infants [25].

Neonatal Bowel Perforation

HSCR presents with bowel perforation about 5 % of the time [26, 27] and HSCR causes about 10 % of all neonatal bowel perforations [28]. Symptoms may not be specific and include poor feeding, emesis, abdominal distension, constipation, diarrhea, and lethargy. In two series with 55 cases reported [26, 27], only one child with perforation was more than two months old. Sixty two percent of the perforations were in the cecum or ascending colon and 15 % were in the appendix. Many of the children with bowel perforation had long-segment disease (34 % total colonic aganglionosis, with an additional 23 % having aganglionosis proximal to the splenic flexure). Since long-segment HSCR is less common than short-segment disease (Table 25.2), proximal colon perforation in a young infant should dramatically raise concern for long-segment HSCR. In 55 % of reported cases, the perforation was proximal to the transition zone in ganglion cell containing bowel. In 13 % the perforation was at the transition zone. In 30 %, however, the perforation occurred in aganglionic bowel distal to the transition zone.

Delayed Passage of Meconium

Delayed passage of meconium should suggest the diagnosis of HSCR, but defining HSCR risk in infants with delayed passage of meconium is challenging because the timing of meconium passage reported for healthy infants is variable. In a study of 979 infants older than 34 weeks gestational age in the United States, 97 % passed meconium by 24 h of life, and 99.8 % passed meconium by 36 h of life [29]. Breastfeeding or bottle-feeding did not influence the timing of the first bowel movement, and multivariate analysis demonstrated that only prematurity was a significant predictor of delayed passage of meconium. A similar study in Turkey [30] also demonstrated that 724/743 (97 %) passed meconium by 24 h after birth and 740/743 (99.6 %) passed meconium by the time that they were 48 h old. However, a smaller study in the Netherlands, reported only 56/71 (79 %) of term infants passed meconium by 24 h after birth [31] and in a study of 267 healthy infants in Nigeria, only 92 % passed their first bowel movement by 48 h after birth [32]. In the Nigerian study, 5 % of the infants were preterm, but even if the preterm infants are excluded, the data suggest that at most 97 % of the healthy full-term infants studied passed their first bowel movement by the time they were 48 h old. Excluding premature infants from the analysis is important since prematurity predisposes to delayed passage of meconium. A study of 611 infants reported that only 57 % of infants less than 29 weeks EGA, 66 % of infants between 29 and 32 weeks EGA, and 80 % of infants between 32 and 37 weeks EGA [33] passed meconium by the end of their "second calendar day" and 1 % of premature infants did not pass meconium until after day of life 9.

In children with Hirschsprung disease, delayed passage of meconium is much more common than in healthy infants. Nonetheless, up to 50 % of children with HSCR pass meconium by 48 h after birth [22, 34, 35], so passage of meconium within 48 h of birth does not exclude a diagnosis of HSCR.

Chronic Severe Constipation

HSCR causes constipation, but constipation unrelated to HSCR is very common (e.g., 25 % of healthy children) and HSCR is rare, so constipation alone usually does not indicate HSCR. "Severe" constipation and constipation beginning within the first few months of life does increase concern for HSCR and the likelihood of disease. For example, in one study, rectal biopsy was performed on all children over a year of age who were referred to a specialty center for consultation and who had constipation refractory to more than 6 months of medical management. Nineteen out of 395 biopsies demonstrated HSCR

Table 25.2 Presenting symptoms in HSCR

Symptom	Comment
Abdominal distension	Very common in HSCR or anatomic bowel obstruction
Bilious emesis	Common and suggests HSCR or anatomic defects
Constipation	Common in older children with HSCR but also in healthy toddlers and infants
Diarrhea	Foul-smelling, bloody, or "explosive" diarrhea suggests enterocolitis (HAEC)
Delayed meconium	Common in HSCR, but many infants with HSCR do not have delayed meconium
Bowel perforation	Should raise concern for HSCR

(5 %), a 250-fold increased risk compared to the population prevalence of HSCR (1/5000) [36]. Constipation in isolation also appears to be an uncommon presentation of HSCR in infants. In particular, the wide range of normal bowel movement frequency in healthy infants makes it difficult to use constipation as the only indication to evaluate for HSCR. In a study of 911 healthy children in Turkey [30] between 2 and 12 months of age, mean stool frequency was once a day, but at 2 months of age, stool frequency varied from once a week to eight times per day.

Abdominal Distension Relieved by Rectal Stimulation or Enema

In children with HSCR, rectal exam or other forms of rectal stimulation may cause a sudden "explosive" release of intraluminal contents and relieve abdominal distension. This is uncommon in other conditions and should raise concern about HSCR. Rectal exam is, however, not otherwise useful in identifying children with HSCR. In particular, "anal tone" is not a reliable indicator of disease.

Enterocolitis

Defining when children have enterocolitis presents its' own challenges (see below for symptoms), but enterocolitis is a dangerous and common presentation for HSCR. When enterocolitis occurs, children with HSCR have diarrhea instead of constipation.

Who Should Be Biopsied to Evaluate for Hirschsprung Disease?

Rectal biopsy is the "gold standard" diagnostic test for HSCR (see below). Unless another diagnosis is evident, children with the following clinical presentations *should undergo* rectal biopsy to evaluate for Hirschsprung disease:

1. Neonates with significant abdominal distension, especially in combination with bilious vomiting or delayed passage of meconium
2. Neonates with bowel perforation

Also *consider* rectal biopsy for Hirschsprung disease in children with:

1. Neonatal bloody diarrhea. Given the low incidence of infectious enteritis in breastfed or formula-fed neonates, bloody diarrhea in neonates is concerning for HSCR-associated enterocolitis (see below). Note, however, that many infants have small streaks of blood in the stool without diarrhea or other symptoms of Hirschsprung disease, and hematochezia alone does not warrant rectal biopsy.
2. Healthy-appearing full-term infants with delayed passage of meconium even in the absence of other symptoms. Since Hirschsprung disease occurs in 1:5000 infants, but delayed passage of meconium for more than 48 h after birth probably happens in at least 1:1000 healthy infants, most children (i.e., >80 %) who have delayed passage of meconium for 48 h will not have HSCR, but the risk of HSCR is probably 5–20 %. Given the risks associated with untreated HSCR, I usually recommend biopsy in this setting. Assuming that 97 % of healthy full-term infants pass meconium by 24 h of life, only about 1:150 children with passage of meconium >24 h after birth, but <48 h after birth will have HSCR. The value of rectal biopsy in this setting is more questionable, unless other symptoms of HSCR are present.
3. Young children with constipation refractory to oral medication. Constipation beginning after a year of age is rarely due to HSCR. Constipation that improves dramatically with oral medication is also unlikely to be due to HSCR. Remember too that the common form of functional constipation that occurs in toddlers may be challenging to treat, usually requiring complete disimpaction and daily maintenance medicine for relief of symptoms, so it can be challenging to know if toddlers are truly "refractory to oral medication."

Red Flags (Conditions That Should Raise Suspicion for HSCR)

1. Constipation with episodes of abdominal distension or vomiting. Constipation does not cause vomiting, but many disorders cause both vomiting and reduced bowel movement frequency including HSCR.

2. Growth failure. This is a common feature of untreated HSCR.
3. Trisomy 21. HSCR occurs in 1–2 % of children with Down syndrome so HSCR should be more readily suspected in children with trisomy 21 [37–39].
4. The presence of additional major anomalies also increases the likelihood of HSCR, but remember that most children with HSCR (>70 %) do not have other medical problems [18, 40, 41].

Given the diverse presenting symptoms of HSCR, it remains difficult to decide who to evaluate. The more "classic" features of HSCR that are present, the more likely the child has HSCR. Given the high morbidity and mortality in untreated HSCR, evaluation for HSCR should be performed in many children who do not end up having this disease to avoid missing this potentially life-threatening medical problem.

Diagnostic Strategies

HSCR by definition means that affected individuals do not have ganglion cells in the distal bowel. Rectal biopsy is therefore required to make the diagnosis and is considered the "gold standard" approach [42]. A number of other strategies for diagnosing HSCR are used, but each has problems.

Rectal Suction Biopsy

This is a simple procedure taking only a few minutes using an instrument designed to take small pieces of the rectal mucosa (e.g., Noblett or rbi2 instrument) to reduce the risk of bowel perforation or hemorrhage [43]. Because there are no sensory nerve endings that respond to cutting in the area of the rectum where the biopsies are obtained, sedation and pain medicines are not required, but sedation is sometimes used in older children. Biopsies should be obtained at 2–3 cm from the dentate line (i.e., the transition between rectal and squamous mucosa) because there is a physiological submucosal aganglionosis in the terminal rectum. From a practical standpoint, however, some authors advocate obtaining biopsies at multiple levels (e.g., 1–3 cm from the dentate line) because precise positioning of the biopsy can be difficult. Biopsy tissues obtained is sectioned, stained, and examined by a pathologist to identify ganglion cells. There is some controversy about the optimal staining method, but hematoxylin and eosin and acetylcholinesterase are commonly used techniques [42, 43]. Calretinin staining might improve diagnostic accuracy [44, 45], but data are still limited. A meta-analysis analyzing data from 993 patients indicated that the mean sensitivity of rectal suction biopsy for HSCR is 93 %, and the mean specificity is 98 % [46]. A more recent manuscript documents 935 cases of HSCR diagnosed by rectal mucosal biopsy (a total of 19,365 biopsies in 6615 children) with no false-positive or false-negative diagnoses (i.e., 100 % sensitivity and specificity) [47]. Serious bleeding and bowel perforation are uncommon with rectal suction biopsy, but can occur. One series of 1340 biopsies [48] reported three bowel perforations (0.2 %), one death (0.07 %), and three rectal hemorrhage (0.2 %) requiring blood transfusion. More recent studies also document low but nonzero rates of serious bleeding or bowel perforation (0 complication in 297 children [49], 0 complication in 88 infants [50], and two episodes of bleeding requiring transfusion (0.7 %) plus one episode of rectal perforation and sepsis (0.035 %) in 272 children) [51]. The most common problem with rectal suction biopsies, however, is that they are so small that they are "inadequate" 6–26 % of the time, requiring repeat biopsy to make a diagnosis [49, 51, 52]. The more recently introduced rbi2 biopsy instrument appears to give a lower frequency of "inadequate specimens" [50] and may give larger biopsies. It is not yet clear if there are also more complications (bleeding or bowel perforation) using the new instrument since large cohort studies have not been published.

Anorectal Manometry

This method tests for the rectoanal inhibition reflex using a small balloon attached to a tube inserted into the rectum [46]. This reflex is absent in children with HSCR. Sensitivity and specificity of anorectal manometry are 91 % and 94 %, respectively, but this test is not required to diagnose HSCR [46]. The equipment needed to do this test is also expensive, and significant experience is needed to evaluate results in infants less than a year of age, so the test is not widely available. Recently developed high-resolution anorectal manometry does not appear to provide increased sensitivity or specificity for HSCR diagnosis (89 % and 83 %, respectively, compared to rectal suction biopsy) [53].

Contrast Enema

This is an X-ray test where images are obtained as contrast is infused into the colon via the anal canal to look for evidence of the distal bowel contraction that occurs in areas of aganglionosis. The change in bowel caliper between contracted distal aganglionic bowel and more dilated ganglion cell containing bowel is called the "transition zone" and suggests HSCR. Although contrast enema may have value in planning the surgical approach to HSCR, the radiographic and anatomic transition from aganglionic to ganglion cell containing bowel may not be in the same location. Note too that in total colonic HSCR, there is no colon transition zone.

Furthermore, the sensitivity (70 %) and specificity (50–80 %) are considerably lower using contrast enema for HSCR diagnosis than other methods [24, 46]. The role of contrast enema in HSCR diagnosis therefore remains a matter of debate.

Full-Thickness Rectal Biopsy

Deeper biopsies can be performed by a surgeon under general anesthesia if the diagnosis remains uncertain after rectal suction biopsy. This method should unambiguously identify enteric neurons if they are present.

Epidemiology/Genetics Overview

HSCR is a multigenic disorder that affects approximately 1/5000 infants. At least 11 specific gene defects are associated with HSCR (*RET, GDNF, NRTN, SOX10, EDNRB, EDN3 ECE1, ZFHX1B, PHOX2B, KIAA1279, TCF4*; reviewed in Chap. 18). For short-segment disease, there is an approximately 4:1 male to female ratio, but for total colonic aganglionosis, the male to female ratio is near 2:1. HSCR has been reported throughout the world in many ethnic groups. There are geographic and racial differences described in HSCR incidence, but these data are difficult to evaluate. Most reports have not been replicated over extended time periods and the difficulty in HSCR diagnosis increases uncertainty in interpreting regional data. Furthermore, it is often not possible to determine from large-scale epidemiological studies the number of affected individuals who share mutations by common descent, so data may be skewed by families with multiple affected members such as has been described in some Mennonite communities [54]. HSCR incidence per 10,000 live births in California was reported as 1.0, 1.5, 2.1, and 2.8 for Hispanics, Caucasian-Americans, African-Americans, and Asians, respectively [55]. HSCR incidence was reported as 1.4 per 10,000 in Denmark, 1.8–2.1 per 10,000 in Japan [11], and 2.3 per 10,000 in British Columbia [56]. Considerably higher rates of HSCR are reported in some small geographic areas or ethnic groups. For example, HSCR incidence is 2.9 per 10,000 in Tasmania [57], 5.6 per 10,000 for native Alaskans [58], 7.3 per 10,000 in Pohnpei State in the Federated States of Micronesia [59], and 5.6 per 10,000 in Oman [60]. In Oman, rates of consanguinity are reported to be high (75 % first or second cousins), but this was not reported in other areas. The European registry (EUROCAT – European Registration of Congenital Anomalies and Twins) also describes striking differences between reporting regions, but ascertainment for HSCR is challenging, and it seems unlikely that the 31 reporting regions use the same ascertainment strategies [18]. Nonetheless, founder effects within populations, nutritional factors, or environmental toxins may account for these differences in HSCR incidence.

Recurrence risk for siblings of children with HSCR is dramatically elevated compared to the general population, but HSCR is a non-Mendelian disease, and risk varies from 1:3 to 1:100 [6, 61] depending on the sex of the proband and their extent of aganglionosis. Because female sex protects against HSCR and because long-segment disease implies more serious genetic risk than short-segment disease, male siblings of females with long-segment HSCR have a 33 % chance of HSCR, while new sisters have only a 9 % risk. Siblings of males with long-segment HSCR have a recurrence risk of 17 % and 13 % in new brothers and sisters, respectively. For a male proband with short-segment HSCR, the risk of recurrence is 5 % in male siblings, but only 1 % in female siblings. For a female proband with short-segment disease, recurrence risk is 5 % and 3 % for new male and female siblings, respectively. These complex epidemiologic and recurrence risk data are a direct reflection of the genetic underpinnings of HSCR. While these "average" data are helpful in discussions with families, far better estimates of HSCR recurrence risk could theoretically be obtained using modern molecular genetic techniques.

Associated Medical Problems

HSCR is an isolated anomaly in ~70 % of affected individuals, but ~30 % of children with HSCR have additional birth defects, including the ~12 % of children with HSCR who have chromosomal anomalies [18, 35, 41, 56, 62–64]. A very wide range of additional defects have been reported in children with HSCR. The most common defects are congenital heart disease, sensory neural problems, kidney and urinary tract, and skeletal anomalies. Many different chromosomal defects have been described in people with HSCR, but trisomy 21 is by far the most common. There are also >30 genetic syndromes associated with HSCR (reviewed in [6, 65]). A few HSCR-associated syndromes are summarized in Table 25.3.

Surgical Management

Although Harald Hirschsprung first described children with the disease that now bears his name in 1886 [66], the pathophysiology of HSCR and management strategies remained unknown until the first successful surgical approach was described in 1948 [67]. There are many modifications of the original pull-through surgery, but the most common procedures today are the Swenson, Duhamel, and Suave endorectal techniques with modification of surgical approaches for total colonic HSCR [1, 14, 68]. For each of these procedures, intraoperative biopsies are obtained to determine the extent

Table 25.3 Selected HSCR-associated syndromes

Syndrome name	Genetic defect	Comments
MEN2A = multiple endocrine neoplasia 2A	RET mutation in codons 609, 611, 618, or 620	~2 % of children with HSCR may have MEN2A RET mutations
FMTC = familial medullary thyroid carcinoma		20–30 % of families with Ret 609, 611, 618, or 620 mutations have members with both FMTC and HSCR
Down syndrome	Trisomy 21	1–2 % of children with trisomy 21 have HSCR
		2–10 % of children with HSCR have Down's
WS4 = Waardenburg syndrome	WS4A = EDNRB	9 % of children with HSCR have WS4
	WS4C = SOX10	Syndrome includes HSCR, deafness, and pigmentary abnormalities
CCHS = congenital central hypoventilation syndrome	PHOX2B	20 % of children with CCHS have HSCR
		0.5–1.5 % of children with HSCR have CCHS
MWS = Mowat-Wilson syndrome	ZFHX1B	60 % of children with MWS have HSCR
		6 % of children with HSCR have MWS
		Syndrome includes HSCR, intellectual disability, epilepsy, dysmorphic facial features, and brain and heart defects
Goldberg-Shprintzen megacolon syndrome	KIAA1279	Syndrome includes HSCR, intellectual disability, dysmorphic facial features, and brain and heart defects
CHH = cartilage-hair hypoplasia syndrome	RMRP	Syndrome includes short stature (dwarfism), other skeletal defects (short limbs), fine sparse hair, and immunodeficiency
		~9 % of children with CHH have HSCR
		CHH is rare in children with HSCR

of aganglionosis. The Swenson procedure involves complete resection of the aganglionic bowel with reanastomosis of ganglion cell containing bowel to a 1–2 cm rectal cuff. In the Duhamel modification, ganglion cell containing bowel is brought through the retrorectal space and anastomosed to a segment of aganglionic rectum using a side-to-side anastomosis. In the Suave procedure as modified by Boley, the rectal mucosa and submucosa are removed and the ganglion cell containing bowel is pulled through a muscular cuff of distal aganglionic bowel and then attached within one cm of the anal verge. There are innumerable studies of surgical outcome, but few large-scale systematic comparisons are available [69], so it remains unclear that one procedure is better than another. Over the past decade, there have been three major changes in surgical management. These include laparoscopic surgery, transanal surgery, and increased use of one-step surgical procedures [12, 70–73]. A recent analysis of transanal versus transabdominal surgery suggests that the children who had transanal endorectal pull-through procedures for HSCR had fewer complications and lower rates of enterocolitis [17]. A comparison of single versus multistage pull-through surgery also suggested that children with single-stage surgery tend to do better, but a subgroup of children who are seriously ill with HSCR may do best with multistep surgery [74].

Cost for Initial Management

For children with HSCR, initial hospitalization costs average $100,000 and the hospital stay averages almost a month [75]. Taking into account HSCR incidence and birth rates, estimated cost for initial care of children with HSCR in the United States is at least $86 million/year. This cost estimate does not include the expense of lost work time or other expenses families encounter while caring for an ill child. Estimates also do not include the cost of ongoing care after the initial hospitalization, which in some cases may be significant, especially in children with enterocolitis. For children with aganglionosis extending into the small bowel, long-term parenteral nutrition also adds dramatically to cost and disease morbidity. Finding new ways to treat or prevent HSCR therefore remains desirable.

Enterocolitis

Hirschsprung disease-associated enterocolitis (HAEC) is common, can occur at any time before or after surgery, and is the most frequent cause of death in infants and children with HSCR [76–78]. Death from HAEC occurs because HSCR predisposes to bacterial translocation into the bloodstream that leads to sepsis. Nonetheless, recognizing HAEC is difficult and until recently there was no standard clinical definition for HAEC. In 2009 a consensus of expert surgeons and gastroenterologists developed a systematic scoring system to identify children with HSCR [79]. Components of the score include "explosive" diarrhea, foul-smelling diarrhea, or bloody diarrhea. Additional components include abdominal distension, explosive discharge of gas and stool with rectal exam, reduced peripheral perfusion, lethargy, and fever. Radiographic findings include multiple air fluid levels, distended loops of bowel, sawtooth and irregular mucosal lining, pneumatosis, and rectosigmoid cutoff sign with the

absence of distal air. Laboratory finding include leukocytosis and a left shift. Many of these features are also listed as presenting symptoms for HSCR because HAEC is common in children with HSCR, especially before surgery.

The reason that children with HSCR develop HAEC is not clear, but enterocolitis does not occur in children with "severe" functional constipation. Possible predisposing factors for HAEC in children with HSCR include residual partial bowel obstruction, defects in epithelial integrity, or abnormalities in the mucosal immune system [78, 80]. Partial obstruction may result from stricture or from intestinal dysmotility causing increased intraluminal pressure and possibly changes in gut flora [81]. Epithelial dysfunction may occur because enteric neurons and glia support normal bowel epithelial cell function and mucin production [82–90]. Problems with intestinal immunity may occur because the ENS directly regulates the adaptive and innate intestinal immune system [91–93]. This includes effects on diverse immune system cells by the ENS neurotransmitters vasoactive intestinal peptide (VIP), neuropeptide Y (NPY), calcitonin gene-related peptide (CGRP), acetylcholine, substance P, and serotonin [94]. Furthermore, some genes that are mutated in children with HSCR have roles in the immune system. For example, RET is important for Peyer's patch formation [95] and immune cell function [96, 97], while EDNRB is important for normal spleen development [98]. Recent work also highlights close interaction between the ENS and macrophages in the muscle layers of the bowel [99, 100]. Given the diverse genetic underpinnings of HSCR and important roles for the ENS controlling intestinal motility, blood flow, epithelial function and immune system function, it seems likely that diverse mechanisms lead to HAEC.

Optimal methods to treat or prevent HAEC are not yet known. Current treatment includes bowel rest, nasogastric tube drainage, intravenous fluids, decompression of dilated bowel via rectal dilation and/or rectal irrigation with normal saline, and the use of broad-spectrum antibiotics [80]. Routine rectal irrigation [101] and long-term metronidazole treatment in children at high risk of enterocolitis may further reduce the frequency of HAEC episodes. Probiotics might also reduce HAEC frequency [102], but beneficial effects are not consistently reported [103] suggesting the need for more investigation. Because HAEC is potentially fatal, it is critical that families understand symptoms of enterocolitis and that plans are in place for prompt treatment should these symptoms arise.

Long-Term Outcome

HSCR is a deadly disease, but outcome with modern surgical methods and improved medical management strategies is dramatically better than in the past. Nonoperative management leads to very high mortality rates (e.g., >50–80 %), and reports from the 1970s describe mortality rates of 25–35 % [14, 104] even with surgical treatment. HSCR death rates today remain about 2–6 % despite modern therapy in large part attributable to enterocolitis [10, 11, 35, 105, 106]. Enterocolitis occurs commonly both before and after surgery for HSCR (25–45 % of children) [17, 75, 107, 108]. Long-term outcome even years after surgery also remains less than ideal with only 45–89 % having normal bowel function. Many individuals continue to have soiling (4–29 %), constipation (3–22 %), or permanent stomas (7–10 %) [109–111]. Normal bowel function is even less common in children with Down syndrome (34 %). Bowel function appears to improve as children get older with "normal" continence in 58 % at 5–10 years after surgery, 68 % at 10–15 years after surgery, and 89 % at 15–20 years after surgery in one study [111]. In this analysis, however, 7 % had marked limitation in their social life 5–10 years after surgery, but this problem improved as children became older.

Lessons from Mouse Models

There are many mouse models with distal bowel or total intestinal aganglionosis that mimic human HSCR [3, 84, 112–117]. This includes mice with mutations in *Ret, Sox10, Ednrb, Edn3, Ece1, Phox2b, Zfhx1b, Sall4, β(beta)1 integrin, Hoxb5, Pds5A, Pds5B, Pax3, Ihh, Raldh2*, and *Pax3*. Recent mouse studies also suggest that excess collagen VI may underlie increased HSCR risk in Down syndrome [118]. Overexpression or inactivation of many additional genes also affect ENS structure or function without causing distal bowel aganglionosis including *Nrtn, Gfra2, Gdnf, Tcof1, L1cam, Shh, Nt3, Ntrk3, Ascl1, Spry2, Dcc, BMP4, Noggin, Raldh1, Raldh3 Celsr3, Fzd3, Kif26a, Lgi4, Phactr4, Tlx2, Tph2, Net, Hoxa4, Gli1, Erbb2, Hand2, Met, Pofut1, Pten, Tfam, Tlr2, Tlr4, Gas1, Smo, Gnaz,* and *Hlx1*. These observations support human genetic data about HSCR causing mutations and also provide additional insight into disease pathogenesis. Mouse models are particularly valuable because they provide direct evidence that specific genetic defects cause specific anomalies. There are a few simple lessons from these model organisms that are relevant to human clinical disease. First, the ENS is often abnormal in the proximal bowel of mice with distal bowel aganglionosis [119], suggesting that many of the ongoing problems in children with HSCR occur because the "normal" proximal bowel is not really normal. Furthermore, areas in the distal bowel that contain ganglion cells may be profoundly hypoganglionic, a problem that is not apparent with the limited biopsies that are obtained during surgery for children with HSCR. Finally in some mouse models, ENS anatomy is nearly normal, but function is profoundly abnormal [120] emphasizing that even sophisticated pathological methods may not provide the information

needed to optimize intestinal function. There are human correlates to these observations in mice including the observation that functional bowel motility problems of the stomach, small bowel, and esophagus apparently are common in humans with HSCR [121–125].

The Future of Hirschsprung Disease

Outcomes for children with HSCR today are quite good, but many challenges remain. The primary problems and opportunities include:

1. *There have been major advances in our understanding of the genetic underpinnings of HSCR, but these findings are not yet routinely incorporated into clinical practice*. Furthermore, there is no consensus about what type of molecular genetic testing, if any, should be performed on children with HSCR. One reasonable argument is that all children with HSCR should be tested for RET mutations that cause MEN2A, but this is still not common practice. As genetic testing becomes less expensive and the capacity to test for many mutations simultaneously increases, it may become practical to perform more comprehensive analysis that would provide information about the risk of other medical problems. It is important that we develop user-friendly methods to understand the type of complex genetic data that are relevant for children with HSCR.
2. *Enterocolitis remains a common cause of morbidity and the most common cause of mortality in children with HSCR. We need a more complete understanding of factors that predispose to HAEC and new ways to prevent this problem*. More research is needed to understand the impact of the ENS on mucosal integrity and on immune system function. We also need more information about whether specific HSCR predisposing mutations increase the risk of HAEC and how differences in gut microbes impact enterocolitis frequency and severity. Most importantly we need to know if there are factors that can be modified to reduce HAEC frequency or severity. Are there changes in surgical approach that would help? Would probiotics be useful? Are there additional medicines that could reduce HAEC rates? Would a more systematic analysis of pathology at the time of surgery help? These questions need to be investigated in more detail.
3. *We need improved methods to evaluate and visualize the ENS*. Acousto-optic spectral imaging [126] and optical coherence microscopy [127] permit visualization of the ENS in mice, but the thicker human bowel wall may make it challenging to visualize the ENS without getting closer to the cells of interest. This may be possible in a minimally invasive way using endoscopic ultrasound to guide needle-based instruments into the bowel wall. For example, after injection of a fluorescent contrast agent (NeuroTrace®), a needle-based laser-induced endomicroscopy instrument visualized the ENS in live pigs [128]. The ability to visualize the ENS without biopsy could potentially make surgery faster and provide better data about the location of the anatomic transition zone. These data might improve surgical outcomes and reduce postsurgical HAEC rates by enhancing the surgeon's ability to evaluate the density of enteric neurons in the bowel intraoperatively.
4. *We need to determine if there are ways to reduce HSCR occurrence rates or to reduce the extent of aganglionosis in affected individuals*. New data from model systems suggest that many environmental factors, including maternal vitamin A levels, mycophenolic acid, and ibuprofen, might impact the likelihood that children develop HSCR [129–131]. Reports of monozygotic twins discordant for HSCR also suggest that HSCR is not a purely genetic disease [35, 41, 132, 133]. Large-scale epidemiological studies coupled with work in model systems should be pursued to identify maternal medicines, health conditions, or nutritional problems that could be modified to prevent HSCR.
5. *We need to find new ways to replace or repair the damaged ENS to rebuild the ENS when development is abnormal*. Recent very exciting studies suggest that stem cell therapy might provide substantial benefit for treating ENS defects [134], but many obstacles need to be overcome for stem cell replacement therapy to become a practical treatment strategy. One promising approach transplants gut-derived ENS progenitors to the bowel after in vitro culture [135–137]. These cells integrate into the ENS and form functional enteric neurons and glia. Recent studies also provide a method to convert human embryonic stem cells (hESC) or induced pluripotent stem cells (hiPSC) into ENS precursor-like cells. These hESC-derived cells can prevent death in a murine HSCR model after transplantation [138]. This work suggests that autologous stem cell therapy using iPSC might be an alternative to pull-through surgery for HSCR if safety concerns could be addressed (e.g., risk that transplanted cells will become neoplastic). Several other sources of cells are being tested for beneficial effects in HSCR models [134]. As an alternative to stem cell therapy, 5-HT4 agonists appear to induce regeneration of the endogenous ENS and might be beneficial in specific settings [139].

Summary

Over the past century dramatic advances have been made in Hirschsprung disease diagnosis, surgical management, developmental biology, and genetics. Ongoing studies provide

new hope that we will be able to reduce HSCR incidence, prevent HAEC, replace missing enteric neurons using stem cells, image the ENS intraoperatively, improve surgical techniques, and incorporate genetics into clinical practice.

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26 Motility Problems in Developmental Disorders: Cerebral Palsy, Down Syndrome, Williams Syndrome, Autism, Turner's Syndrome, Noonan's Syndrome, Rett Syndrome, and Prader-Willi Syndrome

Massimo Martinelli and Annamaria Staiano

Cerebral Palsy

Cerebral palsy (CP) refers to a group of chronic, nonprogressive disorders of movement, posture, and tone due to central nervous system (CNS) damage occurring before cerebral development is complete. The prevalence of CP is approximately 2/1000 live births. The different types of CP vary from series to series, with the spastic type being the most frequent, while periventricular leukomalacia and/or cortical/cerebral atrophy represents the main neuropathological correlates [1]. The survival of children with severe neurological disorders, such as cerebral palsy, has created a major challenge for medical care. Gastrointestinal (GI) motor dysfunction, such as gastroesophageal reflux disease (GERD), dysphagia, vomiting, and chronic constipation, is known to occur frequently in children with different degrees of CNS damage. The degree of GI dysmotility seems to correlate with the degree of brain damage [2]. Swallowing disorders are common in patients affected by CP. In a study by Del Giudice and colleagues, the authors found that 30 of 35 patients with CP presenting with dysphagia had swallowing disorders. The majority of patients showed dysfunction of the oral phase of swallowing with abnormal formation of the alimentary bolus, due to either uncoordinated movements of the tongue or it being contracted and rigid. Alternatively, they had a normal bolus but substantial defects in its propulsion toward the oropharynx, due to the lack of finely coordinated movements of the tongue against the palate. Swallowing disorders have significant implications for development, nutrition, respiratory health, and GI function of this group of patients [3]. The development of dysphagia is associated with a progressive reduction of food intake and represents the main pathogenic factor for malnutrition [4]. Swallowing disorders can also cause recurrent episodes of pulmonary aspiration. For all these reasons, it is essential to diagnose these conditions as early as possible. Videofluoroscopic swallow studies are considered to be a valuable diagnostic tool for children with CP, given their ability to assess both pharyngeal motility and airway protection during swallowing. There is growing evidence that the method of feeding is an important variable in outcomes of children with more severe CP. In those patients with dysphagia, undernutrition, and associated respiratory diseases, the implementation of gastrostomy tube feeding is recommended [5–7]. The American Academy of Cerebral Palsy and Developmental Medicine considers gastrostomy feeding as a valuable alternative nutritional source in this group of children [6]. GERD is very common in patients with a severe neurologic impairment. The prevalence is reported to be between 70 and 90 %, depending upon the different investigations used, including esophageal pH studies and/or upper GI endoscopy [3, 8]. The pathogenesis of GERD in children with CP seems to relate mainly to the impaired motility of the esophagus. Del Giudice et al. demonstrated that most of the patients with neurological handicaps affected by GERD showed prolonged gastric emptying and abnormal esophageal motility. The main abnormalities consisted of significantly lower than normal amplitude of the lower esophageal sphincter (LES) and esophageal peristalsis and an increased number of simultaneous waves, compared to control children (Fig. 26.1) [3]. These findings, part of a more generalized dysmotility of the GI tract, together with other predisposing factors often present in these children, such as spasticity, prolonged supine position, scoliosis, seizures, and reduced amounts of swallowed saliva consequent to drooling, increase the predisposition to the development of GERD and may be responsible for a high failure rate of both medical and surgical treatments. The ideal therapeutical approach to GERD in CP patients is still controversial. According to

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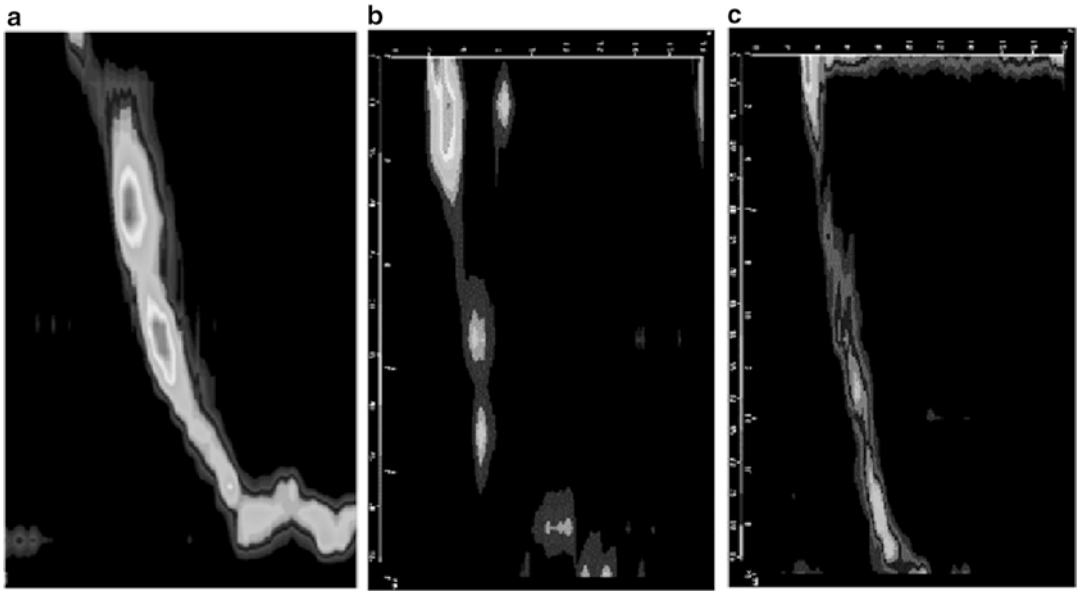

Fig. 26.1 Examples of high-resolution esophageal manometry tracings in a control subject (**a**) and in two patients (**b**, **c**) affected by cerebral palsy. Note in (**a**) a normal esophageal tracing, whereas in (**b**) hypotensive lower esophageal sphincter and low amplitude contraction. In (**c**), marked hypomotility of the smooth muscle region is recognizable

the recent guidelines from the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition and the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN–NASPGHAN) on gastroesophageal reflux, antisecretory therapy should be optimized. Long-term treatment with proton pump inhibitors (PPIs) is often effective for symptom control and maintenance of remission. Baclofen may be used to control vomiting [9]. An alternative medical approach is represented by the use of an elemental diet. We described a lower incidence of GERD in neurologically impaired children with refractory esophagitis treated with amino acid-based formula [10]. However, conventional medical management is less effective in neurologically impaired children. At the same time, surgical intervention is associated with high operative risk given the often suboptimal physical condition of the patients. The benefit/risk ratio of antireflux surgery in patients with persistent symptoms despite optimized medical therapy is not clear. The Nissen fundoplication has been associated with several complications in neurologically impaired children. Postoperative morbidity rates are up to 50 %, reoperation rates up to 20 %, and mortality is substantial [11, 12]. Recently, the advent of laparoscopic Nissen fundoplication has become the procedure of choice. Esposito and colleagues reported a 30 % rate of postoperative complications and 6 % rate of reoperation [13].

Constipation represents another frequent and often undiagnosed problem in patients with CP. The prevalence of the chronic constipation varies from 25 to 75 % in patients with CP [3]. Chronic constipation is often the result of prolonged colonic transit, which is secondary to the underlying gut dysmotility. Colonic transit time seems to be delayed predominantly in the left colon and rectum [14]. It has been suggested that disruption of the neural modulation of colonic motility may play an important role in the development of constipation in children with neurologic diseases. The low fiber and fluid intake and the frequent delay in diagnosis certainly contribute to the development and the persistence of constipation in neurologically impaired children. Staiano et al. demonstrated the efficacy of dietary fiber glucomannan in improving bowel frequency in children with severe brain damage, despite no measurable effects on delayed colonic transit [15].

Down Syndrome

About 77 % of neonates affected by Down syndrome (DS) present with or develop GI abnormalities [16]. Cleves et al., in a recent cohort study, showed an elevated relative risk for GI malformations (OR 67.07) in infants with DS [17]. The most frequent GI malformation associated with DS is Hirschsprung disease; however, esophageal atresia, tracheoesophageal fistula, duodenal atresia or stenosis, and imperforate anus are all well-described associations. Some of the most commonly GI symptoms reported by patients with DS are dysphagia for liquids and solids, vomiting/GER, and heartburn, as well as other esophageal dysmotility symptoms [18]. Children affected by DS are at high risk of GERD [19] and its serious complications such as oropharyngeal aspira-

tion and pneumonia. Much like in other conditions with neurological impairment such as CP, treatment of GERD in DS should combine optimization of antisecretory therapy and behavioral interventions including feeding and positional changes. Despite correct and aggressive medical therapy, some patients with DS, especially patients with respiratory complications of GERD, need antireflux surgery [20]. It has been observed that neurological impairment and GI disease necessitating surgery are independently associated with poorer developmental outcome [21]. In regard to esophageal motor disorders, different cases of association between achalasia and DS have been described, and although achalasia remains a rare entity, it should be considered in any patient with DS who presents with dysphagia [22]. Severe chronic constipation is also highly prevalent [23]. In children with chronic constipation, it is important to exclude Hirschsprung disease (HSCR), observed in approximately 1 out of 200–300 patients with DS [24]. About 30 % of HSCR patients have a recognized chromosomal abnormality, a recognized syndrome, or additional congenital anomalies, the most frequent of which being indeed DS [25]. Moore et al., studying a population of 408 HSCR patients, reported a prevalence of 3.2 % of DS [26], suggesting a possible role for chromosome 21 in the etiology of HD. Nevertheless, the existence of trisomy 21 although seemingly increasing the risk of developing HSCR does not invariably lead to its occurrence. Several studies investigating the role of chromosome 21 as a potential candidate area for a modifying gene in HSCR exist [27], but in the last few years, the possible role of genes mapping outside chromosome 21 (such as SOD1, ITGB2, protein s-100 beta) is emerging. Also, well studied has been the relationship between the major susceptibility genes associated with HSCR (RET and EDNRB) and DS. Arnold et al. [28] demonstrated that the RET enhancer polymorphism RET 19.7 at chromosome 10q11.2 is associated with HSCR in individuals with DS. Interestingly, the RET19.7T allele frequency is significantly different between individuals with DS alone (0.26 ± 0.04), HSCR alone (0.61 ± 0.04), and HSCR and DS (0.41 ± 0.04), demonstrating an association and interaction between RET and chromosome 21 gene dosage. Similarly, a novel EDNRB variant was identified in DS patients with HSCR [29]. There appears to be a significantly higher overall incidence of both pre- and postoperative enterocolitis in DS with HSCR [30].

Williams Syndrome

Williams syndrome (WS), also known as Williams-Beuren syndrome, is due to a homozygous deletion of a contiguous gene on the long arm of chromosome 7 (7q11.23) [31]. The estimated prevalence of WS is 1 in 7500 live births [32]. Most individuals with WS (99 %) have a 1.5 megabase deletion in 7q11.23 encompassing the elastin gene (ELN) and 25–35 other genes, all of which are detectable by fluorescent in situ hybridization (FISH) [33]. Clinical features of WS include distinctive facial anomalies; congenital heart defects, in particular supravalvular aortic stenosis; slight to severe mental retardation; hernia; growth deficiency; and infantile hypercalcemia [34]. Gastrointestinal symptoms such as chronic abdominal pain, feeding problems, constipation, and GERD are seen relatively frequently in children with WS [35]. Hypercalcemia may contribute to irritability, vomiting, constipation, and muscle cramps; it is more common in infancy but may recur in adults [36].

Autism

Autism spectrum disorder (ASD) is a neurodevelopmental condition that unfolds in the first few years of life and involves severe impairments in social interaction and communication, with restriction in interests and extreme attachment to routine or to repetitive or perseverative behaviors [37]. The term includes autistic disorder, Asperger disorder, and pervasive developmental disorder not otherwise specified [37]. Estimates of ASD in pediatric populations have dramatically increased over the past decade, with ~1 in every 88 children meeting diagnostic criteria in the United States [38]. GI dysfunction is frequently reported among children with ASD, and many causal and therapeutic theories of ASD involve the GI system [39]. This includes the hypothesis that a specific GI pathology is associated with ASD, triggered by abnormal immune function or elevated intestinal permeability. A great amount of controversy has surrounded this issue since a publication in 1998 naming a new pathologic entity, "autistic enterocolitis," as responsible for developmental regression in 12 children after administration of the measles-mumps-rubella (MMR) vaccine [40]. Ultimately, this research was retracted for several reasons, including questionable research practices, as found by the General Medical Council of the United Kingdom [41]. Although the presence of a unique GI pathophysiology specific to ASDs has yet to be identified, elevated risk for GI symptoms in this population remains a critical issue in pediatric settings, because this population is significantly more likely to use GI agents and experience hospitalizations related to GI disturbances. The prevalence of GI symptoms in children with ASDs is poorly understood, and it is still unclear whether it is increased when compared with control subjects. Indeed, prospective well-controlled studies are unavailable. To date, prevalence has been reported with a wide range from 9 to 70 % [42–44]. A recent meta-analysis investigating GI symptoms among children with ASD concluded that ASD patients experience significantly more general GI symptoms than comparison groups (mean difference: 0.82, OR: 4.42) [45]. The most common GI symptoms

reported in children with ASDs are chronic constipation, abdominal pain with or without diarrhea, and encopresis as a consequence of constipation [39]. Other gastrointestinal motility abnormalities that have been described for individuals with ASDs include GERD and abdominal bloating [39]. In children with ASDs, gastrointestinal conditions can present typically or atypically as non-gastrointestinal manifestations, including behavioral changes. Horvath et al. reported disturbed sleep and nighttime awakening in 52 % of children with ASDs who had gastrointestinal symptoms (vs 7 % of age-matched healthy sibling) [42]. Children with ASDs who had reflux esophagitis exhibited unexplained irritability more frequently (43 %) than those who did not (13 %) [42]. Behavioral changes may be markers of abdominal pain or discomfort in individuals with ASDs [46]. Nevertheless, a consensus report on the evaluation, diagnosis, and treatment of GI disorders in individuals with ASDs published in 2010 concluded that the existence of a gastrointestinal disturbance specifically correlated with ASDs has not been established [39]. Well-designed trials are therefore needed in order to develop evidence-based recommendations for optimal diagnostic and treatment strategies in children with ASDs. Until then, current consensus is that application and, when necessary, adaptation of conventional recommendations for the general pediatric population are also relevant to children with ASDs [39].

Turner's Syndrome

Turner's syndrome (TS) affects about 1 in 2000 live births females [47]. In about 50 % of cases, karyotype analysis of peripheral lymphocytes reveals the complete loss of one X chromosome (karyotype 45,X) whereas the remaining patients display a multitude of chromosomal abnormalities, including part absence of one X chromosome or mosaicism [47]. In the early 1980s, Chen et al. reported a high incidence of feeding difficulties in early childhood in children affected by TS, associated with regurgitation and vomiting [48]. In 1992, Mathisen and colleagues investigated 10 infants affected by TS and 10 control girls in order to detect oral-motor dysfunction and feeding disorders [49]. Through the use of video recording of routine meals and the administration of the Feeding Assessment Schedule (FAS), the authors clearly demonstrated that patients affected by TS presented considerable and persistent early feeding problems correlated with a characteristic range of oral-motor dysfunctions [49]. Breast-feeding as well as introduction of solid foods was especially difficult for the mothers of case infants. In addition, most of the case-group mothers reported vomiting and regurgitation, suggesting that some children with Turner's syndrome may have some dysfunction of the lower gastroesophageal tract [49]. Following these findings, Staiano and colleagues evaluated upper gastrointestinal motility in patients with Turner's syndrome in order to detect the presence of GI motor dysfunctions [50]. The study population consisted of 13 girls with TS and two comparison groups: seven girls with familial short stature and eight control girls. All the subjects underwent a scintigraphic gastric emptying study. In addition, six girls with TS and eight control children also underwent esophageal manometry [50]. The percentage of retention of solids at 60 and 90 min was significantly greater in patients with TS than in control subjects and in children with familial short stature. Five of the 13 girls with Turner's syndrome had a gastric emptying at 60 min exceeding the mean plus 2 standard deviations of the results in control children. Conversely, esophageal manometry did not show significant differences in TS children when compared with controls group. The authors concluded that the impaired gastric motility represented a novel gastrointestinal finding of this syndrome. To the best of our knowledge, no further report of motility dysfunction in TS children has successively been published.

Noonan's Syndrome

Noonan's syndrome (NS) is an autosomal dominant disorder characterized by short stature, typical face dysmorphology, and congenital heart defects. The incidence of NS is reported to be between 1 in 1000 and 1 in 2500 live births [51]. Severe feeding difficulties are commonly described in children with NS, although the prevalence and underlying cause are poorly understood [52]. In 1992, Sharland and colleagues reported the clinical characteristics of 151 children affected by NS. Feeding histories were obtained in 144 children. Significant feeding difficulties were reported in 75 % of children [52]. In 24 % of these patients, these difficulties were defined as severe, requiring tube feeding for 2 weeks or longer. In 38 % of cases, feeding difficulties were moderate, defined as very poor suck, with slow feeding and recurrent vomiting [52]. Following these early reports, in 1999 Shah et al. conducted a study in order to characterize gastrointestinal motility in children affected by NS [53]. Twenty-five children with NS were consecutively enrolled. Poor feeding described as poor suck or refusal to drink or eat solids, and recurrent vomiting were present in 16 patients. Eight of 16 infants with gastrointestinal symptoms had evidence of gastroesophageal reflux [53]. The children with the most severe symptoms were further investigated by surface electrogastrography (EGG) and antroduodenal manometry (ADM). Four of the five patients who underwent EGG had evidence of abnormal gastric myoelectrical activity. ADM showed an immature contractile activity rather than neuropathological in appearance, reminiscent of that seen in neonates of 32–35 weeks' gestation [53].

Rett Syndrome

Rett syndrome is a neurodevelopmental disorder characterized by a period of developmental regression at approximately 6–18 months with loss of hand and communication skills, development of hand stereotypies, and impaired gait [54]. Most cases are caused by a mutation in the MECP2 gene [54]. As with other neurodevelopmental conditions, disorders of GI motility such as GERD, constipation, and abdominal bloating are common [55]. Recently, a group of experts published a systematic review of the literature in order to provide some practical recommendations for the management of GI motility disorders in children with Rett syndrome [56]. GERD has been reported up to 39 % of girls and women affected by Rett syndrome [57]. According to the experts' panel, common presenting symptoms include vomiting, rumination, regurgitation, and respiratory signs, and unexplained weight loss [56]. The diagnostic approach should not differ from other patients with GERD, including pH-monitoring and upper GI endoscopy. Regarding the treatment, the majority of the panel agreed that conservative strategies such as small frequent feeds and the use of more upright positions in combination with pharmacological management should be adopted [56]. Laparoscopic fundoplication should only be advised in case of refractory GERD. Despite the frequency reported to be up to 80 % of girls and women in a recent US family survey [57], there remains a paucity of evidence as to how constipation should be best diagnosed and treated. Diagnosis is often difficult due to the communication challenges. A stepwise plan for management was identified with a high rate of agreement from the panel members on the use of various laxative agents [56]. Abdominal bloating, as a result of aerophagia, has been reported in almost half of the cases in a population-based sample [58]. In some case reports, severe aerophagia has been associated with gastric perforation [59]. Use of simethicone or magnesium sulfate or selective serotonin reuptake inhibitors has been suggested. There was no consensus on the use of magnesium sulfate; its use has only been supported by case reports. Where symptoms are severe, a gastrostomy may be considered [56].

Prader-Willi Syndrome

Prader-Willi syndrome (PWS) is a multisystemic genetic disease which was first described in 1956 [60]. The incidence of PWS is 1:15,000–30,000 newborns. The syndrome is characterized by muscular hypotonia, feeding difficulties, failure to thrive, developmental delay, short stature, and hypogonadism [60]. Gastrointestinal motility in children with PWS has been sparsely investigated. Following case reports describing gastric rupture in PWS children [61, 62], Arentz and colleagues measured the gastric emptying in eight pediatric patients with PWS through nucleotide scintigraphy after a standardized test meal [63]. In contrast with adult literature [64], the authors found a delayed emptying in 5 out of 8 children and concluded that this may represent a risk factor for the development of gastric rupture [63]. More recently, Kuhlmann et al. evaluated colorectal function in 21 adult patients with PWS [65]. All enrolled patients underwent a whole assessment for diagnosis of constipation including total gastrointestinal transit time (GITT). Eight out of 21 patients fulfilled diagnostic criteria for functional constipation, and GITT was >3 days in 24 % of PWS and none of the controls. To the best of our knowledge, no pediatric study has evaluated the prevalence of functional constipation among PWS children.

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Familial Dysautonomia and Mitochondrial Disorders

27

Massimo Martinelli and Annamaria Staiano

Familial Dysautonomia

Familial dysautonomia, also known as Riley-Day syndrome, is an autosomal recessive disorder, which occurs predominantly in the Ashkenazi Jewish population with an incidence of about 1 in 1370 individuals. It is associated with a complex neurological disorder that affects the sensory system and the autonomic nervous system functions [1]. Although FD is caused by one gene and the penetrance is always complete, there is a great deal of variation in expression. The sensory dysfunction is characterized by alterations of small fiber neuronal populations such that patients with FD have impaired sensations of temperature, pain, and vibration. The autonomic dysfunction affects multiple systems, and it is characterized by cyclic manifestations of typical "dysautonomic crisis"; these crisis represent systemic reactions to physiologic and psychological stress. Gastrointestinal perturbations such as vomiting are the predominant part of the constellation of symptoms seen during an episode; other symptoms include hypertension, tachycardia, diaphoresis, personality changes, blotching of the skin, piloerection, functional ileus, and dilatation of pupils [2]. Malfunction of the GI tract is the main clinical manifestation of FD with oropharyngeal incoordination being one of the earliest symptoms in the newborn. Discoordinated swallow is found in about the 60 % of patients with FD, and it is often responsible for the development of severe feeding alteration, malnutrition, and recurrent aspirations, which can lead to chronic lung disease [3]. Impaired brainstem reflexes seem to underlie these abnormalities [4]. Videofluorographic swallow studies allow for visualization of bolus flow throughout the upper aerodigestive tract in real time, and it is used to examine the presence and the timing of aspiration. In addition, cineradiographic swallowing studies may document the level of functional ability [5, 6]. However, the most prominent GI symptom is the propensity to vomit. Recurrent vomiting can be caused by peripheral as well as central autonomic dysfunction. Vomiting can occur cyclically as a part of dysautonomic crisis or daily in response to stress of arousal. When the vomiting is associated with a constellation of symptoms including hypertension, tachycardia, and diffuse sweating, the symptom is secondary to the autonomic crisis. The efficacy of diazepam in reducing vomiting during autonomic crisis suggests that the crisis is caused by a central phenomenon, probably developed from autonomic seizures [7]. Gastroesophageal reflux is another common problem. Sundaram and colleagues found a prevalence of 95 % of GERD in a sample study of 174 patients with FD [8]. Clinical symptoms can range from regurgitation to more atypical manifestations such as wheezing, apnea, or iron deficiency anemia secondary to severe esophagitis. A major contributor to the development of GERD is represented by the dysfunction and the increased relaxation of the lower esophageal sphincter (LES). The LES is controlled by postganglionic parasympathetic fibers within the vagus nerve and preganglionic sympathetic fibers. The parasympathetic circuits are able to control both the relaxation and the contraction of LES, while the sympathetic system evokes exclusively the contraction. The pathogenesis of GERD is correlated to the reported degeneration of sympathetic and the consequent prevalence of the parasympathetic nervous system. Thickened fluids and smaller, more frequent meals represent the first steps in management. Medical management includes use of H2-antagonists and proton pump inhibitors. However, if symptoms persist and events such as hematemesis occur, surgical intervention (such as a fundoplication) is strongly recommended. Up to 80 % of patients with FD undergo fundoplication surgery [9, 10]. The impact of the fundoplication wrap on the natural history of these patients compared with that of untreated patients has not been clarified. GERD can reoccur after the fundoplication, and up to 12 % of patients who receive the procedure require a second surgery [11]. Esophageal dilatation and achalasia are possible recognized complications after fundoplication surgery [12, 13].

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Mitochondrial Disorders

Mitochondrial disorders (MD) refer to a clinically heterogeneous group of disorders that arise as a result of a dysfunction of the mitochondrial respiratory chain. They can be caused by either inherited or spontaneous mutations of nuclear (nDNA) or mitochondrial DNA (mtDNA) which lead to altered functions of the proteins or RNA molecules that normally reside in mitochondria. Defects in nDNA can be inherited from either parent, while defects in the genes of the mtDNA are maternally inherited. Mitochondria are present in virtually all cell types of human body, and their damage affects especially the main energy-dependent tissues such as the brain, heart, liver, skeletal muscles, kidney, and the endocrine and respiratory systems [14]. MD primarily affect children, but adult onset is becoming more recognized. Over 100 mtDNA abnormalities associated to MD have been described in the literature, some resulting in profound disability and premature death [15]. Gastrointestinal symptoms are reported in 15 % of patients with MD occurring usually in childhood, before the onset of more classical extraintestinal symptoms of MD [16]. The major MD presenting with GI symptoms are mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) (peripheral neuropathy, ophthalmoparesis, leukoencephalopathy, muscle wasting, cachexia) [17], Leigh syndrome (subacute necrotizing encephalomyelopathy resulting in hypotonia, bulbar paresis, abnormal eye movements, lack of coordination of extremities, and regressive psychomotor development) [18], Kearns-Sayre syndrome (chronic progressive external ophthalmoplegia, atypical pigmentary retinopathy, ataxia, and heart block) [19], and MELAS syndrome (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes) [20]. MNGIE is a rare autosomal recessive disorder caused by mutations in the gene-encoding thymidine phosphorylase (TP), which lead to absolute or nearly complete loss of its catalytic activity, producing systemic accumulations of its substrates, thymidine (dThd) and deoxyuridine (dUrd) [21]. MNGIE typically presents between the first and third decades with GI symptoms as presenting feature in approximately half of the cases [22]. All patients will eventually develop GI symptoms during the course of the disease. Main symptoms attributable to GI dysmotility include dysphagia, early satiety, nausea, vomiting, abdominal pain and cramps, borborygmi, intestinal pseudo-obstruction, and bloating. These symptoms invariably lead to weight loss, which may manifest as extreme cachexia. Although the average age at presentation is approximately 18 years, GI symptoms have been reported earlier during the first year of life, including diarrhea at 5 months of age in one case and intussusception at 8 months in another infant [22]. Different mtDNA mutations have been associated with GI disorders in MD. Recently Horvath et al. found a new heteroplasmic mutation in the anticodon-stem of mitochondrial tRNA of a girl presenting with clinical symptoms of MNGIE-like GI dysmotility and cachexia [23]. Intestinal pseudo-obstruction is an increasingly recognized clinical feature in MNGIE and represents an important cause of chronic intestinal failure. The pathogenesis of intestinal pseudo-obstruction in MD is still unclear. Giordano et al. described the presence of smooth cell atrophy, mitochondrial proliferation, and mtDNA depletion in the muscularis propria of small intestine in two different studies, performed in one and four patients suffering from MNGIE, respectively [24, 25]. Their pathogenetic hypothesis is that the baseline low abundance of mtDNA molecules may predispose smooth muscle cells of the external layer of muscularis propria to the toxic effects of circulating dThd and dUrd. More recently, Zimmer et al. reported an alteration of the interstitial cells of Cajal (ICC) network in MNGIE [26]. These findings support the hypothesis that ICC loss might be an early pathogenetic event in MNGIE-associated gut motor dysfunction before significant myopathic and/or neuropathic structural changes occur [26]. Poor feeding and vomiting are often the initial presenting symptoms in Leigh syndrome [27, 28]. Mutations in more than 40 mtDNA and nuclear-encoded genes have so far been linked to this condition. Mutations in the nuclear gene-encoding SURF1, a mitochondrial protein involved in cytochrome c oxidase assembly, have been noted in many patients with Leigh syndrome and GI symptoms [29]. Dysphagia is also common in patients affected by Leigh syndrome [30]. Dysphagia seems to be due to primary esophageal dysmotility, neurogenic causes, or a combination of these two factors. Fifteen percent of patients with Kearns-Sayre syndrome, a MD characterized by progressive cytochrome c oxidase deficiency, presents with swallowing difficulties and dysphagia [31]. Shaker et al. described the manometric characteristics of a cervical dysphagia in a patient with Kearns-Sayre observing the absence of pharyngeal peristalsis, abnormally low upper esophageal sphincter resting pressure, and the absence of proximal esophageal peristalsis [32]. Eighty percent of patients with MELAS have the same mtDNA mutation, m.3243A>G, while the remaining cases are caused by a range of other mtDNA mutations. Diagnostic criteria include a stroke-like episode occurring before 40 years, neurological disturbance characterized by seizures and/or progressive dementia, lactic acidosis, and a ragged-red fibers myopathy [33]. Other neurological features include severe migraines, sensorineural hearing loss, peripheral neuropathy, and psychiatric problems including depression. Gastrointestinal problems have been frequently reported in children affected by MELAS. Sproule et al. reported at least one GI disturbance in 64 % of a prospective cohort of 45 patients with a diagnosis of MELAS [34]. Symptoms included abdominal discomfort, vomiting, constipation, diarrhea, gastroparesis, intestinal pseudo-obstruction, and recurrent pancreatitis [34]. Other MD are characterized by nonspecific GI symptoms including dysphagia, delayed gastric emptying, feeding difficulties, GERD and/or vomiting, diarrhea, failure to thrive, and abdominal pain [35]. GI symptoms are predominantly localized in the

upper GI tract. Chitkara et al. reported the cases of six children with MD who presented upper GI symptoms such as vomiting, food aversion, poor suck, and feeding intolerance [36]. Dysmotility disorders like delayed gastric emptying and intestinal pseudo-obstruction have been reported in children and adult patients with MD. Gastroparesis has been associated with various diseases and may occur as part of a MD [37, 38]. There is no consensus regarding management of patients with gastroparesis who do not respond to simple antiemetic or prokinetic therapy. Tatekawa et al. proposed a new surgical technique in a 12-year-old girl with pyruvate dehydrogenase complex deficiency with refractory gastroparesis [39].

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Part IV

Motility Disorders After Surgery and Developmental Anomalies of the Enteric Neuromuscular System Secondary to Anatomical Malformations

Esophageal Atresia

28

Franziska Righini Grunder and Christophe Faure

Esophageal atresia (EA) with or without tracheoesophageal fistula is the commonest congenital digestive anomaly, occurring in 1 in 2400–4500 births worldwide [1]. Since the first successful surgery in 1941, anesthetic, surgical, and neonatal care have improved tremendously, and care issues have shifted the focus from mortality to short- and long-term morbidity and quality of life issues [2]. Besides respiratory symptoms, motor disorders of the esophagus leading to gastroesophageal reflux (GER), esophageal stricture, feeding disorders, and dysphagia remain the most frequent associated problems. In the long-term, potentially related to chronic acid exposure of the esophageal mucosa, Barrett's esophagus and esophageal carcinoma are also a concern. International recommendations on management of gastrointestinal and nutritional complications in children with EA have been recently published [3].

Associated Problems After EA Repair

Gastroesophageal Reflux

After EA repair the prevalence of GER is reported between 22 and 63 % depending upon the patients' age, EA type, and diagnostic techniques or criteria. In infants and children with isolated EA (type A), GER is reported in almost all patients. GER is often associated with complications such as esophagitis as well as recurrent anastomotic stricture as suggested by noncontrolled studies [4–6]. Respiratory complications (persistent atelectasis, aspiration pneumonia, asthma/increased airway reactivity, chronic lung disease with bronchiectasis and worsened tracheomalacia, airway obstruction, and/or acute life-threatening episode) may also be associated with GER [4, 6]. However, pulmonary symptoms can also be related to aspiration of mucus or food retention in the proximal pouch or distal esophagus, anastomotic stricture, congenital esophageal stenosis, aspiration during swallowing, recurrent or missed fistulae, eosinophilic esophagitis, or esophageal pooling above a fundoplication.

Using impedance testing in 24 children with EA, Fröhlich et al. demonstrated an abnormal bolus index in 67 % of the patients [7]. Catalano et al. studied a group of 22 children with EA at a median age of 15 months with an uneventful postoperative course: reflux episodes were mainly non-acidic (76.4 % of total refluxes), especially in children younger than 1 year (89.2 %) [8]. Pathological acid reflux was reported in 10 of 22 patients (45 %). One of the limitations of pH-impedance testing in patients with EA is that baseline impedance is lower than control patients because of poor esophageal function and/or stasis of liquid especially in the lower esophagus [7, 9]. Therefore, a careful manual analysis, in addition to automated analysis, is critical in these patients.

Patients with EA are at a high risk of developing severe GER for several reasons: esophageal dysmotility, hiatal hernia, smaller portion of the intrathoracic part of esophagus, surgical injury to the vagus nerve, and abnormal gastric motility. A combined impedance-manometry study conducted in ten children aged less than 3 years with noncomplicated type C EA reported that transient lower esophageal sphincter (LES) relaxation was the pathophysiological mechanism in 2/3 of the reflux episodes [10]. No similar data are available for long-gap EA, and these data may not apply to patients with high-tension anastomosis leading to abnormal anatomic location of the LES as well as impaired esophageal motility. Recent recommendations suggest that GER be systematically treated with proton pump inhibitors (PPIs) for prevention of peptic complications and anastomotic stricture up to the first year of life or longer, depending on persistence of GERD [3].

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Dysphagia

Studies have reported that dysphagia is very common occurring in 21–84 % of infants, children, and adults with EA after surgical repair [11–15]. A recent systematic review found an overall pooled estimated prevalence of 50.3 % in patients older than 10 years [16]. Dysphagia is probably more prevalent than reported, because children may not recognize their symptoms as abnormal and may appear better adapted to their unique situation [13]. Since there is no specific symptom, dysphagia should be suspected in patients with EA who present with food aversion, food impaction, difficulty in swallowing, odynophagia, choking, cough, pneumonia, alteration in eating habits, vomiting, and malnutrition. Children may have minor or occasional difficulties with swallowing, may eat slowly or drink excessive amounts of liquids with foods, or develop recurrent food impactions. Significant changes in eating habits are reported in up to 73 % of patients with dysphagia (need to drink, change in diet, last to finish meal) [13].

A step-by-step investigation of dysphagia warrants a barium swallow and an upper endoscopy with biopsies [3]. The etiology of dysphagia may include inflammatory or anatomic causes such as peptic esophagitis, eosinophilic esophagitis [17], anastomotic stricture, congenital stenosis [18], peptic stricture, post-fundoplication obstruction, vascular anomalies [19], anastomotic diverticulum [12, 20], and mucosal bridge [21]. In the absence of the latter causes, esophageal dysmotility remains the most likely culprit.

Feeding Disorders

Aspiration of retained food or mucus above or below the anastomosis may occur because of stricture or dysmotility possibly related to abnormal innervation to the proximal pouch or distal esophagus [22, 23].

The evaluation of aspiration during swallowing is very important to pursue as 20–47 % of children with EA have aspiration or penetration [24, 25]. If aspiration is identified, the differential must include laryngeal clefts, vocal cord paralysis, a neurologic etiology including Chiari malformations, and developmental delay in swallowing function. Studies of patients with EA suggest that 3–17 % have clinically significant vocal cord paralysis and, while the incidence of laryngeal cleft in patients with EA is not known, 27 % of laryngeal cleft patients have EA [26–28].

Esophageal Motility in Patients with EA

Esophageal dysmotility has been reported in almost all patients with EA but does not correlate with symptoms of dysphagia. Esophageal motility has been assessed in children by either esophageal manometry (either water-perfused [10] or high-resolution solid state [13, 15, 29]), impedancemetry [30], or videofluoroscopy [31].

Upper Esophageal Sphincter

The UES function has been reported to be normal by most authors [13, 15], but incomplete relaxation has been described in newborns [32]. When evaluated by videomanometry, an inadequate coordination between pharyngeal contraction and UES relaxation was found in adults [31]. Aspiration during swallowing assessed by videofluoroscopy has been reported in 20–47 % of children with EA [24, 25].

Esophageal Body

Esophageal body dysfunction has been reported in nearly all patients with EA. It is found in children [10, 13, 15, 29, 32–37] and persists throughout life as demonstrated by adult studies [12]. Using high-resolution manometry, the patterns of esophageal dysmotility in children with EA were recently described, and motility was reported abnormal in all patients, with three types of abnormalities observed: aperistalsis, isolated distal contractions, and pressurization (Fig. 28.1a–c) [13]. Consistently, the pattern of esophageal dysmotility was not predictive of the presence or severity of dysphagia. Impedance coupled to high-resolution manometry now allows to categorize the pattern of esophageal dysmotility and to correlate the degree of motility abnormalities with bolus transit (Fig. 28.1d). This may prove to be critical because the correlation between dysphagia, motility abnormalities, and bolus transit is imperfect.

Symptoms related to GER are prominent in patients with aperistaltic esophagus [13, 29]. There are no prospective longitudinal studies of patients with EA reporting the natural history of esophageal dysmotility. Using conventional manometric technique in 101 adults, Sistonen et al. demonstrated non-propagating peristalsis with weak and simultaneous esophageal pressure waves in 80 % of patients, with ineffective distal esophageal peristalsis in all. Manometrical abnormalities were significantly worse in those with epithelial metaplasia [12].

Lower Esophageal Sphincter

In most studies, including those using high-resolution manometry, LES function is generally similar to controls [13, 15, 20, 32, 33, 38, 39]. A study conducted in children with noncomplicated type C EA reports that transient LES relaxation is the main pathophysiological mechanism in 2/3 of the reflux episodes [10].

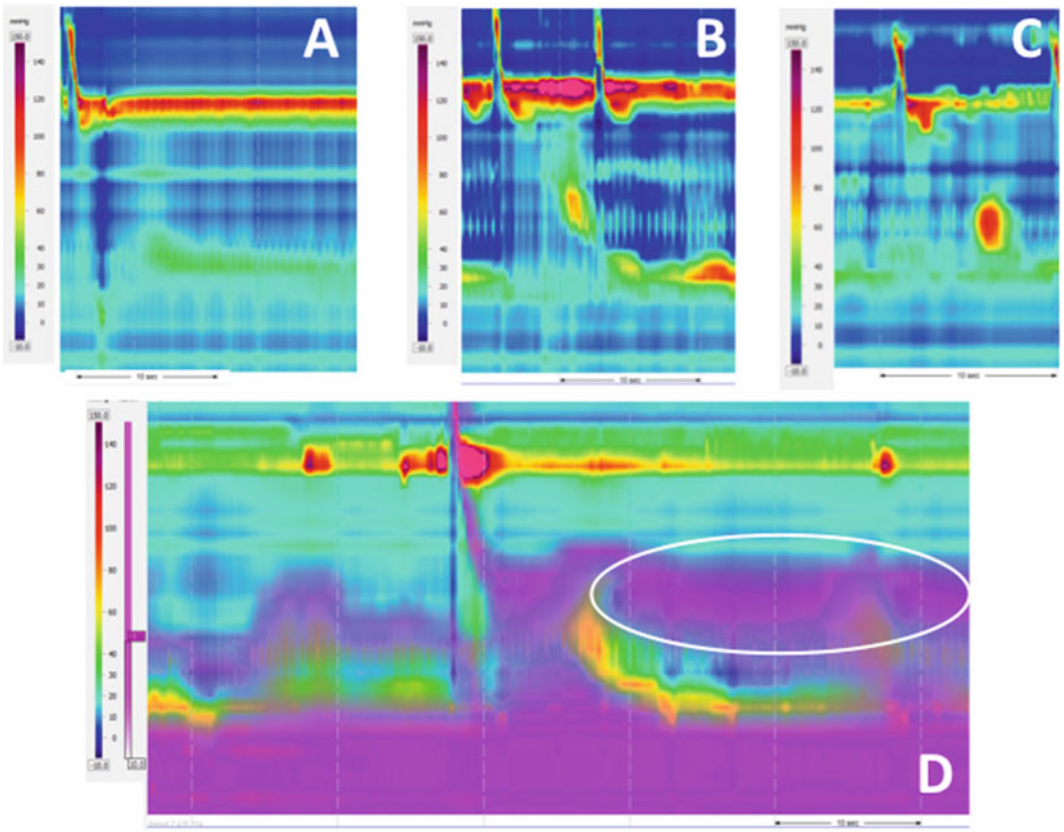

Fig. 28.1 High-resolution esophageal manometry tracings recorded in patients with esophageal atresia. Aperistalsis pattern (**a**); distal (weak) contraction patterns (**b**, **c**). (**d**) A liquid swallow studied by high resolution/impedance in a patient with a type C esophageal atresia. Note the distal weak peristalsis with abnormal bolus clearance. The *white circle* depicts residual liquid (*purple*) in the esophagus

Etiology of the Esophageal Dysmotility

The etiology of the esophageal motor disorder remains unclear and controversial. It may be caused by (1) intrinsic factors related to abnormal development of the esophageal smooth muscle and intrinsic innervation and vagus nerve or (2) operative maneuvers and postoperative complications. Data indicating a key role of the congenital malformation are gaining strength.

Primary Motility Disorder of the Esophagus

In patients with EA, the key role of the abnormal development of esophageal innervation and musculature in esophageal dysmotility is supported by several lines of evidence. Romeo et al. have reported an esophageal manometry study in 20 newborns with EA and have demonstrated motor abnormalities in the proximal (pouch) and distal esophagus prior to surgery [32]. Similarly, abnormal esophageal motility patterns have been described in children and adults with isolated TEF without atresia before surgical repair [40].

Pathological data support also the role of abnormal intrinsic and vagal innervation of the esophagus. Detailed analysis of esophageal intrinsic innervation in deceased newborns with EA reported abnormalities in the Auerbach plexus (plexus hypoplasia, abnormal interganglionic network) [41]. Other studies found hypoplasia of esophageal innervation or smooth muscle [42] in the proximal pouch [43], in the distal esophagus [22, 23], or in the fistula [42, 44]. Findings on adriamycin-induced EA fetal rat model have similarly shown an abnormal distribution of nerve tissue in the esophagus [45] and inherent abnormalities in the branching pattern of the vagus nerves [46].

Postsurgical Dysmotility

On the other hand, the dysmotility may also be secondary to the dissection during surgery damaging vagal nerve and its esophageal branches [22]. However, unilateral vagotomy has no effect on peristalsis, presumably because of extensive crossover of vagal innervation within the esophageal wall [47]. Surgery may also result in an extensive mobilization and denervation of the esophagus. Shono et al. demonstrated

in two patients with pure EA studied before surgery a coordinated peristalsis between the proximal and the distal esophagus as well as a normal LES reflex relaxation suggesting that surgery may alter the esophageal motility [48]. However, this is not supported by experimental animal studies where transection and anastomosis of the esophagus did not cause severe esophageal dysmotility [49].

Antireflux Procedure in Patients with EA

Nissen fundoplication may worsen the symptoms of esophageal dysmotility, and careful attention must be considered when such procedure is indicated [3]. The wrap creates a mechanical obstruction for those patients with an abnormal esophageal motility leading to a potential exacerbation of the dysphagia secondary to the combination of reduced esophageal motility and a tight wrap and outflow obstruction at the wrap level. Current recommendations suggest that antireflux procedure may be considered if, despite maximal medical therapy, there is life-threatening or life-limiting symptoms (recurrent esophageal strictures, poorly-controlled GERD despite maximal PPI therapy, long-term dependence on transpyloric feeding, dying spells) [3].

Gastric Motility in Patients with EA

Romeo et al. reported that 36 % of patients with EA have delayed gastric emptying on scintigraphy and 45 % abnormal gastric peristalsis activity on manometry [50]. Using ^{13}C-octanoate gastric emptying breath test, Van Wijk et al. reported 57 % of a small cohort of children having a gastric emptying time >90th % [10].

Dumping syndrome is often unrecognized and its diagnosis delayed. In children with EA, it is most often encountered after a fundoplication or in patients with microgastria [51]. It has also been reported in patients with EA with no other precipitating factors [52]. Whether gastric motility disorder may be primitive or secondary to vagus nerve injury is unknown.

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Anorectal Malformations

29

Ann Aspirot

Anorectal malformations (ARM) are a spectrum of congenital abnormalities of the terminal portion of the hindgut which lies partially or completely outside the anal sphincter mechanism. In these conditions, the gastrointestinal tract ends blindly or opens ectopically to the skin or the genitourinary tract (fistula). They affect about 1 in 5000 live births worldwide [1] with a slight male predominance. It is not always possible to correct completely these anomalies and long-term consequences with impacts on quality of life are frequent.

Classification

In 2005, an international conference for the development of standards for the treatment of ARM took place at Krickenbeck, Germany [2]. During this workshop, 26 international experts on congenital malformations of the organs of the pelvis and perineum reviewed the recent advances and developed an international classification for ARM (Table 29.1). The most frequent defects in male and female are, respectively, rectourethral fistula and vestibular fistula. In the past, the Wingspread classification subdivided the anomalies into low, intermediate, and high anomalies according to the level of the rectal pouchin relation to the levator ani muscles. This older classification is important to know in order to understand the older medical literature on the subject and to have an idea of the expected functional outcome: the highest the anomaly, the worst is the prognosis for fecal continence. Generally, ARM without perineal fistula are grouped under the high forms, and those with a perineal rectal opening are considered low forms [3] (Fig. 29.1a, b).

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Etiology

The etiology of ARM is unclear, but it is assumed to be multifactorial. In the animal models and human studies, genetic and environmental factors were identified. ARM have been induced in mice and rats by in utero exposure to Adriamycin, etretinate, and ethylenethiourea [4]. Some studies have suggested a link to in vitro fertilization [5] and maternal diabetes mellitus [6, 7]. No single gene or chromosomal locus has been identified. However, the frequent association with other congenital anomalies and genetic syndromes (Table 29.2) [8, 9] strongly supports a genetic component. Familial incidence has been shown in non-syndromic or isolated ARM, especially with the perineal and vestibular fistulas. Cloaca and rectoprostatic fistulae are less likely to have affected family members. The recurrence risk for rectovestibular and perineal fistulae is 3–4 % for full siblings and approximately 2 % for first-degree relatives [9].

Embryology

The embryology of many congenital anomalies in humans is still not completely understood and recent studies are questioning the traditional theories. ARM is an example and several animal models have been developed to better characterize it.

Abnormal development of the cloaca rather than a persistent stage of normal embryology is the hypothesis for most of the ARM [4]. In the normal embryo, the cloaca is formed around the third week of gestation. It consists of a common cavity into which the hindgut (rectum), the allantois (bladder), and the mesonephric ducts (Wolffian) open cranially. Caudally, the cloaca ends as the tail gut. The cloacal membrane extends vertically and anteriorly from the allantois to the tail gut. As a result of the ventral growth of the genital tubercle, the shape of the cloaca changes and the cloacal membrane swings to a horizontal position. A urorectal fold

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(or urogenital septum) situated between the allantois and the hindgut descents caudally until it meets the cloacal membrane. This descent results in the separation of the urethra and the rectum and in the disintegration of the cloacal membrane at that area (seventh week of gestation). The dorsal cloaca in the tail region remains fixed and will constitute the anal orifice. In ARM animal models, unusual shape of the cloaca, too short cloacal membrane (absent dorsal parts), and abnormal junction between the proximal hindgut and the cloaca were found (Fig. 29.2).

Table 29.1 International classification of anorectal malformations (Krickenbeck)

Major clinical groups	Rare regional variants
Perineal (cutaneous) fistula	Pouch colon
Rectourethral fistula	Rectal atresia/stenosis
(a) Bulbar	Rectovaginal fistula
(b) Prostatic	H fistula
Rectovesical fistula	Others
Vestibular fistula	
Cloaca	
No fistula	
Anal stenosis	

From Holschneider A, Hutson J, Pena A, Beket E, Chatterjee S, Coran A, et al. Preliminary report on the International Conference for the Development of Standards for the Treatment of Anorectal Malformations. J Pediatr Surg. 2005;40(10):1521–6, with permission

The muscles surrounding the anorectum develop at the same time and are composed of three parts: the external sphincter, the puborectalis muscle, and the internal sphincter [10, 11]. The external sphincter appears first, followed by the puborectalis muscle which appears before 10 weeks of

Table 29.2 Syndromes with anorectal malformations

Syndrome/association	Genetic anomaly
VACTERL association	
Down	Trisomy 21
Patau	Trisomy 13
Edwards	Trisomy 18
Cat eye	Trisomy/tetrasomy 22
Townes-Brocks	Mutation of SALL1
Currarino	Mutation of HLXB9
Pallister Hall	Mutation of GLI3
X-linked heterotaxy	Mutation of ZIC3
Johanson-Blizzard	Mutation of UBR1
McKusick-Kaufman	Mutation of MKKS
Duane-radial ray/Okihiro	Mutation of SALL4
Bifid nose, anorectal, renal (BNAR)	Mutation of FREM1
Polydactyly, imperforation anus, vertebral (PIV)	

From Mundt E, Bates MD. Genetics of Hirschsprung disease and anorectal malformations. Semin Pediatr Surg. 2010;19(2):107–17, with permission

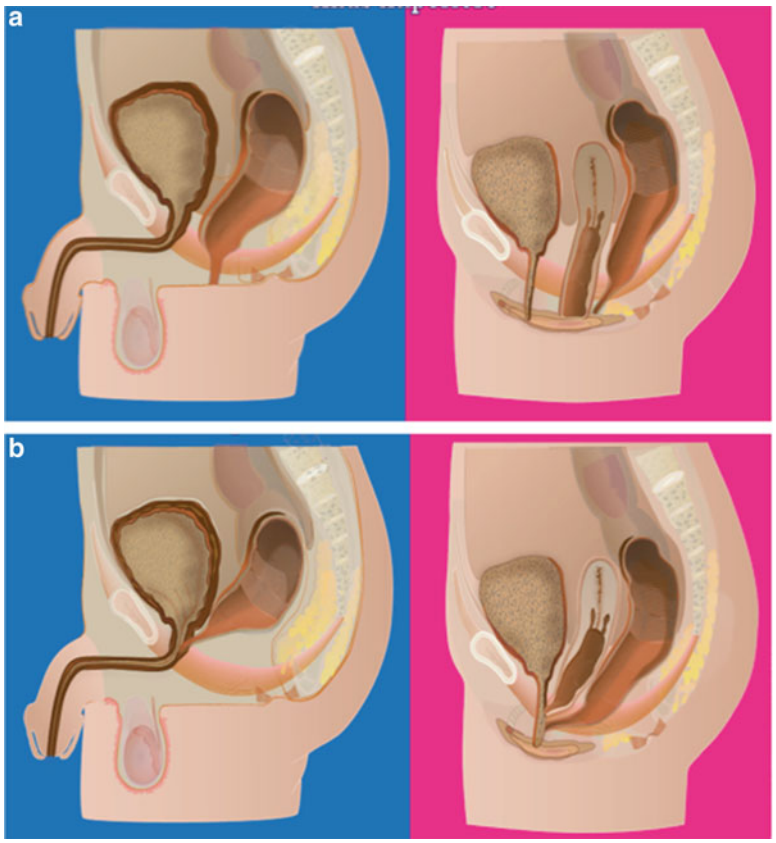

Fig. 29.1 (**a**) Schematization of perineal (male) and vestibular (female) fistula. (**b**) Schematization of rectourethral fistula (male) and cloaca (female). (From M Leduc, Medical Illustration, Sainte-Justine University Health Center, 2014, with permission)

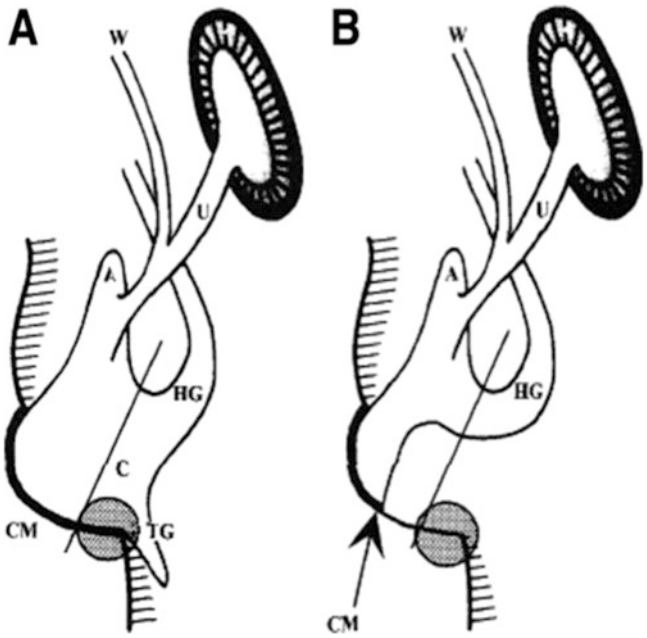

Fig. 29.2 Normal and abnormal cloaca. Schematic drawings of a normal (**a**) and an abnormal (**b**) cloaca. In the abnormal embryo, the cloacal membrane (CM) is too short (*arrow*). The cloacal membrane does not extend to the region of the tail groove (*gray area*). The dorsal cloaca is missing. In the normal embryo (**a**), the cloacal membrane is of normal length and extends to the region of the tail groove (*gray area*). (From Kluth D. Embryology of anorectal malformations. Semin Pediatr Surg. 2010;19(3):201–8, with permission)

gestation and forms a sling around the anorectum. The internal sphincter grows after the rupture of the cloacal membrane and is not well differentiated until 10 weeks.

Associated Malformations

More than 50 % of the newborns with ARM have at least one associated anomaly [12]. The higher forms are even more likely to have more other anomalies. The severity of these associated anomalies is variable from incidental findings to life-threatening conditions. ARM can be part of a syndrome in 3.7 %, a chromosomal anomaly in 11 %, a sequence in 9 % (caudal dysplasia, Potter syndrome, prune belly), or the VACTERL association (vertebral defects, anal atresia, cardiac septal defects, esophageal atresia, renal anomalies, and radial limb defect) in 10 % [8]. Abdominal wall defects, especially omphalocele (OEIS complex: omphalocele, exstrophy, imperforate anus, and spine anomalies), can be associated with anal anomalies in 6.8 %. Associated affected systems include cardiovascular, gastrointestinal, spinal, sacral, vertebral, genitourinary, and gynecologic. *Cardiovascular anomalies* need to be ruled out before the surgical management because they are present in 16–22 % of patients with ARM [13, 14], and they can change the initial management if significant. The most frequent anomalies are atrial septal defect and ventricular septal defect, but more significant malformations such as tetralogy of Fallot, transposition of great vessels, and hypoplastic left heart syndrome are also possible. Many *gastrointestinal anomalies* have been described; the most frequent are tracheoesophageal in 10 % and duodenal with or without malrotation in 1–2 %. Hirschsprung disease is rare in patients with ARM, and the diagnosis must be confirmed with certitude because of the increased risk of fecal incontinence if proctectomy is performed in a context of ARM. *Sacrovertebral anomalies* are the most frequent bony structures defects (hemivertebrae, scoliosis, hemisacrum) and affect about a third of the patients [15]. The co-occurrence of sacral defect (typically hemisacrum), ARM, and presacral mass (teratoma or anterior meningocele) is known as the Currarino triad [16]. It is autosomal dominant with variable expressivity. Hypodevelopment of the sacrum can be quantified by the sacral ratio which is a helpful prognostic tool for continence and is associated with the severity of the ARM [17]. The prevalence of *spinal anomalies* is about 50 % [18] with a wide variety of severity (thickened filum, fibrolipoma, tethered cord, syringomyelia, myelomeningocele). The clinical significance of the occult spinal dysraphism is unclear, but routine detection is recommended in all types of ARM [15, 19]. Untethering of the cord improves the motor function in symptomatic patients, but it does not change the bowel or urinary function [20]. Patients with tethered cord have a worse functional prognosis that is also predictable by the type of ARM and sacral defect, but there is no evidence that prophylactic surgery can change the prognosis [21]. Close clinical follow-up and urodynamic studies are recommended in patients with tethered cord [18]. *Genitourinary anomalies* affect one third to half of patients [22]. Vesicoureteral reflux is the most frequent anomaly, affecting 60 % [23], followed by renal agenesis and dysplasia. In males, 20 % have cryptorchidism [24] and 5 % have hypospadias [22]. Patients with ARM associated with partial sacral agenesis are at increased risk of bladder-sphincter dysfunction and should be assessed by urodynamic studies [25]. *Gynecologic anomalies* have been unrecognized in the past but constitute a significant cause of morbidity on the long term [26]. In girls with rectovestibular fistula, 5 % have a vaginal septum and 9 % an absent vagina [27]. Hydrocolpos can cause a urinary obstruction or pyocolpos in the neonatal period. The absence or underdevelopment of the Mullerian structures can cause obstruction of the menstrual flow at the puberty.

Neonatal Management

A thorough physical examination is of critical importance and will often lead to the diagnosis of the ARM and the associated anomalies [28]. When inspecting the perineum, it is

important to look at the color and aspect of the skin, assess the external sphincter contraction, and identify presence of ectopic anal opening. In boys, the presence of meconium at the meatus or in the urine will automatically confirm the presence of a rectourinary fistula. In girls, a single perineal orifice establishes the diagnostic of a cloaca. In this eventuality, it is mandatory to rule out hydrocolpos and urinary obstruction. In the cases where there is no visible meconium on physical examination, it is important to wait 24 h before labeling the type of anomaly and planning the surgical intervention. In the meantime, the baby should receive intravenous fluids, antibiotics, and nasogastric decompression. Associated anomalies must be ruled out by cardiac echography, renal and spinal ultrasound, and lumbar spine and sacrum plain radiographs. Within the first 24 h of life, if there is evacuation of meconium through a perineal fistula, a primary anoplasty can be performed. If the baby has other life-threatening issues, the fistula can be dilated and the definitive surgical treatment postponed for a few months as long as the rectum is well decompressed. If after 24 h there is no evidence of meconium in the urine or through a perineal fistula, a cross-table lateral radiograph can be performed with the baby in prone position and a marker at the suspected site of the external sphincter in order to assess the level of the rectal gas compared to the pubococcygeal line. A perineal ultrasound can also be performed. A distance between the distal rectal pouch and the perineum greater than 15 mm suggests an intermediate or high ARM [29].

Operative Management

The main goals of treatment in the neonatal period are to relieve the intestinal obstruction and recognize and treat any associated defects that may be life threatening [30]. Relieving the intestinal obstruction can be achieved by definitive repair, anal dilation, or colostomy. Depending on the experience of the surgeon and the patient clinical status, a low form without perineal fistula or a vestibular fistula can be primarily repaired or initially diverted by a colostomy. Some surgeons will also prefer to dilate the vestibular fistula and postpone the primary repair by few months when the plan between the vagina and the fistula has become thicker. A colostomy and delayed definitive repair at 2–3 months is recommended in higher forms (urethral fistula, cloaca) in order to characterize better the anatomy and prevent complications such as urethral injury. In cloaca, drainage of hydrocolpos and urinary diversion may be necessary. The distal colostogram is the best study to assess the anatomy [31]. A voiding cystourethrogram is also indicated to detect vesicoureteral reflux and, when done at the same time, can help to show the position of the rectal pouch compared to the urethra if no fistula is seen on the colostogram.

Table 29.3 International grouping (Krickenbeck) of surgical procedures for follow-up

Operative procedures	Perineal operation
	Anterior sagittal approach
	Sacroperineal approach
	PSARP
	Abdominosacroperineal pull-through
	Abdominoperineal pull-through
	Laparoscopy-assisted pull-through
Associated conditions	Sacral anomalies
	Tethered cord

From Holschneider A, Hutson J, Pena A, Beket E, Chatterjee S, Coran A, et al. Preliminary report on the International Conference for the Development of Standards for the Treatment of Anorectal Malformations. J Pediatr Surg. 2005;40(10):1521–6, with permission

Operative Approaches of the Definitive Treatment

The main goal of the definitive treatment is to anatomically reconstruct the malformations in a way that will avoid complications that may lead to permanent sequelae. Table 29.3 enumerates the possible surgical procedures. Perineal operation is reserved for low forms. All ARM can be repaired by a posterior sagittal anorectoplasty (PSARP) which will be limited to a smaller incision of 1–2 cm in the lower forms. This technique involves a posterior midline division of the structures up to the rectum. It has revolutionized the surgical approach by permitting a better exposition of the anatomy [32]. Cloaca and rectovesical fistula may require an abdominal approach that can be performed open or by laparoscopy [33]. Laparoscopically assisted anorectal pull-through (LAARPT) has gained popularity and offers the advantages of a good visualization of the rectal fistula and surrounding structures, accurate placement of the bowel through the anatomic midline and levator sling, and minimally invasive abdominal wound and perineal dissection [34].

Outcome

Modern surgical techniques and neonatal care have improved the outcomes of all the congenital malformations and ARM are not an exception. Mortality of patients with ARM had been between 10 and 20 % and has decreased to 3 % more recently. It is principally due to the severe associated anomalies. The mortality is about three times higher in patients with high anomalies than in patients with low anomalies [3].

Operative Complications

A colostomy is useful in higher forms to decompress the distal rectosigmoid and assess the anatomy preoperatively [28]. However, it carries a risk of morbidity. Prolapse and stricture

are the most common complications. Specific colostomy complications in ARM patients are related to the position of the colostomy: if too proximal, the rectum may not be well decompressed and megarectosigmoid predisposes to long-term constipation and overflow incontinence. On the other hand, a colostomy too distal needs to be replaced at the definitive repair to allow the rectum to reach the perineum.

Following pull-through, wound infection, dehiscence, and retraction with varying severity may occur. Deeper infection may lead to acquired rectal atresia and/or recurrent fistula requiring reoperation and leading to long-term functional sequelae [35]. Urologic injury is a well-known complication, especially in boys [36]. The risk is decreased with PSARP if an adequate preoperative colostogram is performed [37]. With the laparoscopic approach, the surrounding structures such as bladder, ureter, vas deferens, prostate, seminal vesicles, and urethra are visualized but still at risk for traumatism. Posterior urethral diverticula have more frequently been described in intermediate forms and after laparoscopic repair. Anal stenosis and rectal mucosal prolapse are commonly seen after pull-through. It is thought that postoperative anal stricture is prevented by an adequate anal dilatation program. Contrary to what was previously thought, there seems to be no significant difference in rates of mucosal prolapse between laparoscopic and open approaches [38].

Early Outcome in Childhood

Abnormal bowel function is common. After closure of the colostomy, patients with higher forms of ARM often develop frequent bowel movements causing perineal skin excoriations. This problem will continue to be particularly challenging on the long term if the terminal rectal reservoir has been resected. Constipation is a major problem affecting half of the patients with ARM and it is even more frequent in lower forms of ARM. It needs to be detected and treated aggressively in order to prevent the development of megarectum and pseudoincontinence [39, 40].

Evaluation of Long-Term Functional Outcome

In the literature, there is a great variation in the criteria used to evaluate long-term results after repair of ARM [41]. The multiple scoring methods based on subjective parameters that have been designed to quantify the bowel function have made comparisons among studies difficult [3, 42]. The Krickenbeck outcome classification tried to solve this problem (Table 29.4). This descriptive, nonscoring method is applicable after the age of 3 and permits a uniformization of the report of results [2]. It has been used in most recent publications [43–47].

Table 29.4 International classification (Krickenbeck) for postoperative results

1. Voluntary bowel movements		Yes/no
	Feeling of urge	
	Capacity to verbalize	
	Hold the bowel movement	
2. Soiling		Yes/no
Grade 1	Occasionally (once or twice a week)	
Grade 2	Every day, no social problem	
Grade 3	Constant, social problem	
3. Constipation		Yes/no
Grade 1	Manageable by changes in diet	
Grade 2	Requires laxatives	
Grade 3	Resistant to diet and laxatives	

From Holschneider A, Hutson J, Pena A, Beket E, Chatterjee S, Coran A, et al. Preliminary report on the International Conference for the Development of Standards for the Treatment of Anorectal Malformations. J Pediatr Surg. 2005;40(10):1521–6, with permission

Manometry has been the principal method to assess objectively the postoperative sphincter function. Correlation with clinical results is sometimes conflicting [3]. Clinical continence has been positively correlated with anal resting pressure [48–53], voluntary squeeze pressure [54], and rectal sensitivity assessed by balloon inflation [49, 54, 55]. The presence of the inhibitory rectoanal reflex is also described as a good prognostic factor [48–50, 56]. Colonic motility has also been studied. Hypomotility tended to be localized in the rectosigmoid in low ARM and was more generalized in high ARM [57]. Propagation of excessive numbers of high-amplitude propagating contractions (HAPC) into the neorectum may be a contributing factor to fecal incontinence in patients with repaired ARM [51].

Morphologic evaluation of the sphincter can be performed by echoendosonography [53, 55, 56] or magnetic resonance imaging (MRI) [58, 59]. Echoendosonography visualizes disruption or scar of the sphincters. MRI not only shows the sphincter complex, but it also allows the assessment of the placement of the bowel in relation to the sphincters and the anorectal angle. The predictability of the functional outcome with MRI is not clear [60].

Long-Term Outcome

According to Pena's extensive series of more than a 1000 of patients over two decades, 77 % of patients have voluntary bowel movements by the age of 3 [30]. Half of them soil their underwear occasionally, meaning that only 37.5 % are totally continent. Despite the fact that 25 % are totally incontinent, a definitive repair of all the types of ARM is still recommended because a bowel management program can be effective to treat the fecal incontinence and keep the patients

clean. It is however important to give realistic information to parents about what to expect in the long term since the outcome is related to the severity of the anomaly. Voluntary bowel movements are possible in 90 % of patients with rectal atresia/stenosis, perineal fistula, vestibular fistula, and imperforate anus without fistula. However, total continence is achieved in only half of the vestibular fistula and imperforate anus without fistula. Gender differences have also been noted with less incontinence and constipation in males than in females with perineal fistulas [45]. According to that study, perineal and vestibular fistulas had similar outcomes in girls. Regarding higher forms, voluntary bowel movements are present in 80 % of patients with a short cloaca or a bulbar rectourethral fistula, but only 30 % do not have fecal soiling. Prostatic rectourethral fistula and long cloaca have voluntary bowel movements in 73 and 55 % of cases, but only 45 and 39 % do not have fecal incontinence. Rectovesical fistula has the worst prognostic with 35 % on voluntary bowel movements and no patient without soiling [30].

With the advent of the LAARPT, it became crucial to study the outcome of this technique compared to PSARP. A prospective study of 24 cases of high-intermediate ARM found no differences in sphincter thickness as assessed by echoendosonography and MRI, but the clinical score was better for LAARPT [43]. A randomized control trial (RCT) did not find a difference in clinical outcomes in the short term, but the anal resting pressure assessed by manometry was improved [61]. A systematic review and meta-analysis grouping this RCT and six retrospective cohorts for a total of 187 patients found no difference in rates of defecation scores [38]. However, defecation outcomes were inconsistently reported and some reports included patients younger than 3 years old.

Long-Term Sequela Related to Associated Anomalies

Urinary incontinence from a *neurogenic bladder* is expected after repair of a cloaca but should be rare in male except if there is associated abnormal sacrum or spine [23, 25]. A third of patients with short cloaca require intermittent catheterization and long cloaca require intermittent catheterization in 70–80 % of cases [62]. Patients with cloaca are also at risk for chronic renal failure due to structural anomaly of the urinary tract such as renal dysplasia, ectopic/solitary/duplex kidney, and ureteropelvic junction obstruction. Vesicoureteral reflux and sacral abnormality are present in the majority of them [63].

Fertility does not seem to be affected in low forms of ARM [64], but it is decreased in higher forms [65]. Gynecological problems are usually related to the associated defects and have been discussed earlier. In males, erectile dysfunction, weak or missing erection, and retrograde ejaculations have been reported [65]. Avoidance of *sexual activity* may be chosen by patients because of poor bowel continence (20 of the patients with high anomalies and 13 % of the patients with low anomalies) [64, 65].

Methods to Improve Fecal Continence

Bowel Management Program

Because the fecal incontinence can have disastrous consequences on self-esteem and quality of life, it is ideal to establish a bowel management program before the entrance to school. This program consists of the daily administration of enema by the parents to clean the colon. Before starting it, it is important to understand the physiopathology of fecal incontinence: overflow pseudoincontinence and true fecal incontinence [66]. The differentiation between the two is essential because the treatment is different. Pseudoincontinence is caused by constipation and is suspected in the presence of a history of stool impaction (fecaloma on physical examination or on an abdominal X-ray, dilatation of the rectosigmoid on a barium enema). Colonic motility is decreased as can be demonstrated by colonic manometry or scintigraphy. True fecal incontinence is caused by increased motility, the absence of rectal reservoir, and sphincter failure. It is suspected in cases of diarrhea, when a barium enema shows a non-dilated colon with haustrations going down into the pelvis [30]. In the first group, the treatment consists of large-volume enemas with additives such as glycerin, bisacodyl, or phosphate administrated every night. The second group is easier to clean with smaller volume of saline enemas but will also require a constipating diet and medications to decrease bowel motility (e.g., loperamide) [28]. The bowel management program is generally well accepted by the children, but when they become adolescents, antegrade enema through an appendicostomy or a cecostomy constitute better solutions because they allow a self-administration of the colonic irrigation. Antegrade enemas have been shown to improve quality of life of patients [67].

Surgical Alternatives

In certain selected cases, resection of the dilated distal segment may be successful in treating constipation and fecal incontinence [68], but it can also convert a case of overflow incontinence to one of true incontinence because of the loss of the rectal reservoir. Optimal conservative management seems to have similar bowel functional outcome to the surgical treatment [69]. Redo surgery for mislocation of the rectum can be offered in patients with good prognostic factors, but it

does not necessarily lead to improved fecal continence [70, 71]. Different sphincter reconstructions have been proposed, but the long-term results are not convincing [3].

Other Alternatives

Sacral nerve stimulation (SNS) has shown promising results for children with urinary and fecal incontinence in a randomized crossover study [72]. Etiologies for incontinence were mainly of neurological origin. SNS consists of the surgical implantation of a neuromodulator in the S3 foramen. It is well tolerated by the patients. Other groups are collecting prospective data on that therapy [73]. *Biofeedback conditioning* has also been used to treat fecal incontinence with limited results. It is effective when the functional and morphologic assessment pretreatment is favorable [74]. It may represent an important adjunct to a multidisciplinary behavioral treatment [75, 76].

Conclusion

Despite significant improvements, the results of surgery are not optimal in a significant proportion of patients with ARM and these patients need careful follow-up. Children with ARM are at increased risk for behavioral and social problems. Since there are conflicting results about the correlation of those problems with the level of continence [77, 78], all patients should be followed by a multidisciplinary team including not only physicians but also nurses, psychologists, social workers, physiotherapists, and nutritionists [66]. The benefits of such multidisciplinary behavioral treatment strategy have been established [75, 76].

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Motility After Small Bowel and Colonic Surgery

30

Roberto Gomez and John E. Fortunato

Surgery of the small intestine and colon is commonly performed in children for a variety of indications ranging from congenital anatomic abnormalities to need for enteral feeding access to underlying motility disorders. Under most circumstances, non-emergent operations allow time for a multidisciplinary team approach between surgeons and gastroenterologists to devise a thorough preoperative diagnostic strategy. Unfortunately, abdominal catastrophes such as malrotation with volvulus often preclude the luxury of time before surgery necessitating a strong relationship between surgeon and gastroenterologist to address the potential consequences of such an event. In both cases, the motility of the small bowel and colon remains a critical feature that often predicts the success of an operation and, most importantly, the prognosis of the patient. This chapter aims to address several of the more prevalent motility disorders observed in children after small bowel and colonic surgery.

Small Bowel Motility After Resection

Resection of short or long segments of the small bowel may be necessary for different indications including *surgical emergencies* such as bowel ischemia or necrosis from volvulus and perforation; *congenital anomalies* such as intestinal atresia, malrotation, and gastroschisis; or *acquired etiologies* encompassing stricturing Crohn's disease, ulcerative colitis, severe necrotizing enterocolitis, intestinal pseudoobstruction, or abdominal trauma. New advances in intestinal rehabilitation such as home TPN, lipid solutions, frequent small bowel bacterial decontamination, and new central line technology that decrease the number of line infections dramatically have changed the prognosis of infants after a small bowel resection. Preservation of bowel length, particularly the small intestine, is critical to insure adequate absorption of nutrients, fluids, and electrolytes but is contingent on circumstances such as extent of the necrosis or ischemia. The consequences of a more extensive resection of small bowel include symptoms such as frequent diarrhea, malnutrition, and bloating due to bacterial overgrowth and may result in the need for parental nutrition with its associated complications.

Small intestinal resections are classified into three categories based on length of residual small bowel: short resection with 100–150-cm length remaining, large resection with 40–100 cm remaining, and massive resection with 40 cm or less remaining. In general, massive resections particularly in the context of an absent ileocecal valve are associated with inability to wean completely from parenteral nutrition [1]. The absence of ileocecal valve has been associated with increased diarrhea and small bowel bacterial overgrowth (SBBO).

While mucosal adaptation has been extensively studied, there is a paucity of data regarding changes in motility after small intestinal resection. A better functional outcome is associated with proximal compared to distal resection, which may be related to both the adaptive capacity and intrinsic properties of the jejunum and ileum. Adaptation involves all layers of the bowel wall, including intestinal smooth muscle. The intestinal smooth muscle is coordinated by both hormonal and neuronal components which regulate the transit of intestinal contents through the gastrointestinal tract [2]. Activation of this complex circuitry allows changes in the peristaltic reflex to modulate the intestinal motility pattern from propagative to segmenting. This is accomplished through a complex integration of signals that trigger a jejunal and ileal break mechanism in response to nutrients, most notably fats. Mediators involved in this response include peptide YY, chemosensitive afferent neurons, noradrenergic

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nerves, myenteric serotonergic neurons, and opioid neurons [3]. Following proximal resection of small bowel, for example, it has been demonstrated that the postprandial motilin response is decreased, whereas transient increases in neurotensin and peptide YY have been noted after distal resection [4].

After intestinal loss, a combination of shorter bowel length and disruption of normal physiological mechanisms may lead to poor absorption and malnutrition. Increased contractile response and proliferative changes in intestinal smooth muscle cells may contribute to the compensatory adaptive mechanism to slow intestinal transit and improve nutrient absorption. While the cellular mechanism for this process is not well defined, mechanisms such as epidermal growth factor receptor signaling have been shown to play a role in adaptation of the smooth muscle cellular compartment [2].

Little is known about changes in the migrating motor complex (MMC) after resection. Animal studies often reveal conflicting results with a broad spectrum of motility changes depending on the extent and location of resection. For example, after extensive distal small bowel resection, postoperative changes such as decreased MMC velocity and longer intervals between MMCs during fasting with slight recovery of propagation frequency in the chronic phase have been observed [5, 6]. Findings such as shorter phase I duration and discoordinate clustered MMC activity have also been seen using the same model [7]. There are very limited motility studies in humans after small bowel resection [8–10]. With extensive distal resection, motility changes include shorter duration and more frequent MMCs as well as a reduction in phase 2 activity; however, limited ileal resection does not result in detectable manometric changes of jejunal motility [9]. The postprandial motor response is not well defined, but appears to be shorter in patients after resection [10].

Short Bowel Syndrome Perioperative Evaluation

The goal of surgery for patients with short bowel syndrome include maximizing intestinal absorption, improving motility and transit of the dilated aperistaltic segments, as well as delaying intestinal transit time in some cases. Laparotomy or laparoscopy is also required in some cases to close stomas or address causes of obstruction such as abdominal adhesions [11].

A thorough and focused evaluation must be performed to determine the best surgical option in patients with short bowel. Perioperative evaluation may include assessment of intestinal length and caliber, motility, and intestinal transit. An upper gastrointestinal series with small bowel follow, for instance, can determine bowel anatomy and identify the presence of obstruction leading to possible adhesiolysis or remodeling of an anastomosis [12]. Determination of intestinal transit can also be assessed to some extent with an upper gastrointestinal series; however, the study has several limitations. First, it does not quantitatively evaluate motility. In addition, the chemical composition of the contrast itself may alter motility giving a false impression of the intestinal transit. The authors believe that antroduodenal and colonic manometry are crucial in the study of these patients. Unfortunately, motility studies are not systematically used in patients with short bowel syndrome, especially before operative management. The preoperative value of colonic and antroduodenal manometry in differentiating peristaltic versus aperistalsic bowel segments was recently addressed in a case series [13]. In this series, a normal colonic manometry was the basis for preserving continuity of the colon in a patient with short bowel syndrome. In contrast, abdominal distension and feeding intolerance with absent distal colonic motility markedly improved after placement of a left-sided colostomy in a patient with prior gastroschisis and short bowel syndrome (Dr. J. Balint, personal communication) (Fig. 30.1).

Short Bowel Syndrome Surgical Approaches

Procedures to Alter Intestinal Transit

Delaying the intestinal transit time has been recognized as an important mechanism in order to increase absorption and maximize contact of the nutrients in patients with short gut syndrome. Several procedures have been designed for this purpose. For example, creation of intestinal valves by placing a Teflon collar around the circumference of the bowel, or by everting the small bowel mucosa, creating a small intussusceptum can induce proximal dilatation increasing adaptation [14, 15]. Reversed antiperistalsic segments of intestine have also been proposed as an alternative for delaying intestinal transit. The reversed segment is usually short and is placed as distal as possible to prevent obstruction. This procedure has been used in adults with short bowel syndrome with 50 % of patients being able to wean off total parenteral nutrition [16]. The study was based on previous findings in canine models in which the reversed segment was observed to cause retrograde peristalsis disrupting the motility of the proximal intestine [17]. Colonic interposition has also been used to delay intestinal transit time [18]. However, this study was limited by a small number of patients and lack of perioperative assessment of motility changes.

Dilation of a segment of small bowel is frequently associated with poor motility and presence of bacterial overgrowth. Therefore, increasing motility of the dilated segment has been an important aim in many types of autologous reconstructive

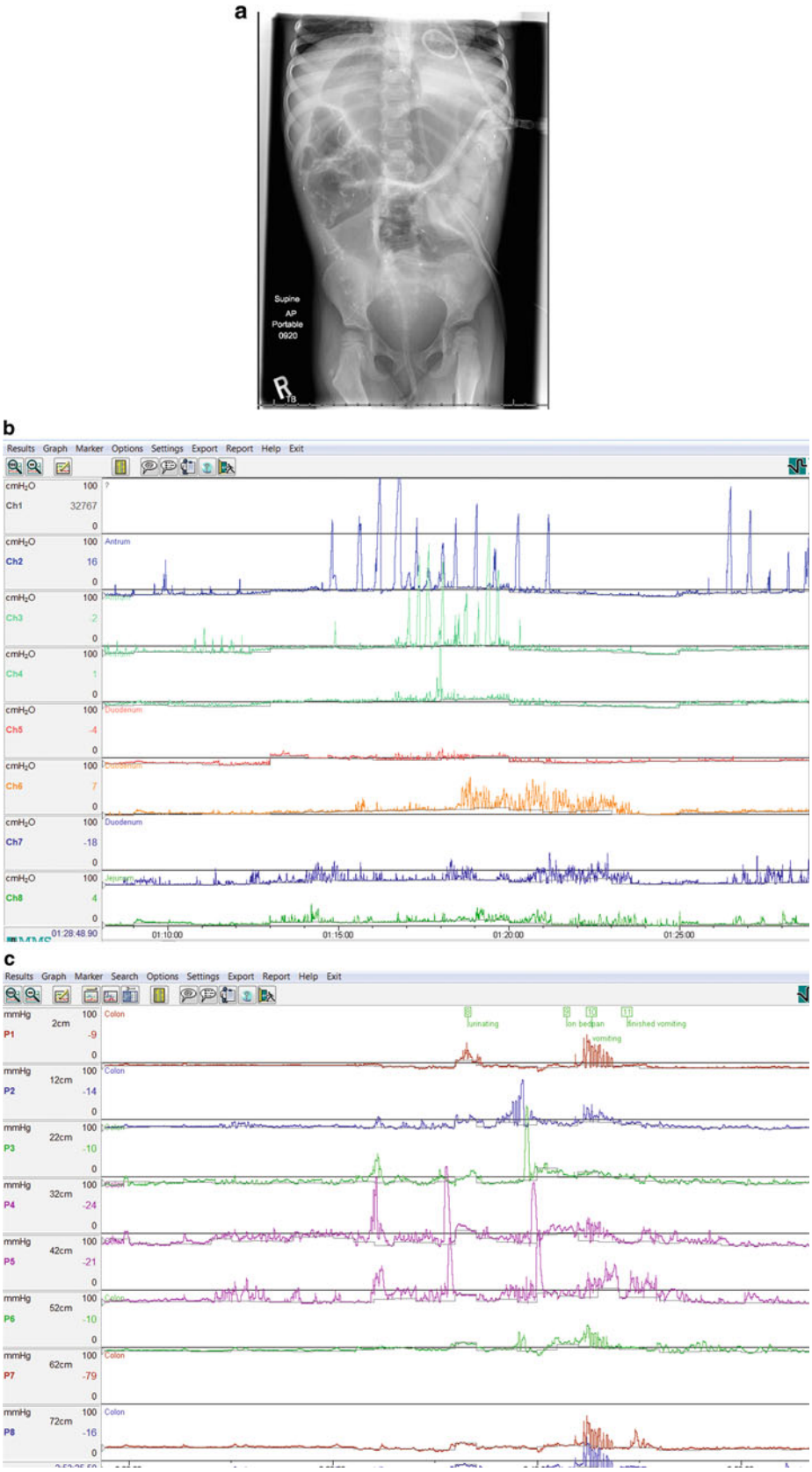

Fig. 30.1 Patient with history of gastroschisis resulting in short bowel syndrome with persistent abdominal distension (**a**) and feeding intolerance after STEP. Antroduodenal manometry demonstrated adequate small bowel motility after STEP (**b**). Absence of motility was shown in the distal colon (**c**). Subsequent placement of a left-sided colostomy resulted in symptom resolution and tolerance of enteral nutrition. (Courtesy of Drs. Gomez and Burns, Nemours Children's Hospital, Orlando, FL)

bowel surgery. Tapering enteroplasty reduces the caliber of the bowel lumen, preserving the length, and thereby improving peristalsis [19, 20]. The impact of this tapering on the different phases of the MMC or postprandial motility indices is not clear.

Intestinal Lengthening

Surgical procedures including longitudinal intestinal lengthening and tailoring (Bianchi's LILT) or serial transverse enteroplasty (STEP) were designed to increase the length of the intestine and maximize absorption in patients with short bowel syndrome [21, 22]. These procedures are usually performed after a period of intestinal adaptation and not immediately after resection. LILT isoperistaltic bowel lengthening entails longitudinal division of the bowel with isoperistaltic end-to-end anastomosis effectively doubling the length of that portion of the bowel. The STEP procedure involves the sequential linear stapling of the dilated small bowel from alternating directions perpendicular to the long axis of the intestine [22].

Both LILT and STEP have been shown to successfully result in increased caloric absorption and preserved intestinal motility [23, 24]. After LILT, there is an increased tolerance of enteral feeds, improved growth, and decreased frequency of catheter infections. Significant improvement in stool counts, intestinal transit time, D-xylose absorption, and fat absorption resulting in discontinuation of parenteral nutrition has also been observed [25, 26]. After LILT, 55–79 % of the patients are able to wean from parenteral nutrition with survival rates up to 77 % [27, 28]. Limitations of the LILT procedure include its technical difficulty, involvement of at least one intestinal anastomosis, and risk to the mesenteric blood supply. It is also best performed if the bowel is symmetrically dilated. Complications such as ileal valve prolapse and recurrent small bowel dilatation have been reported after the operation [24].

STEP has become widely accepted among pediatric surgeons as it is technically easier to perform than LILT and preserves the natural mesenteric vasculature to the intestine [29]. STEP has been shown to improve weight retention, nutritional status, and intestinal absorptive capacity in an animal model. Its results are comparable to LILT with around 80 % of the patients being able to wean off parenteral nutrition [27, 30]. Motility studies performed in a STEP animal model suggest that the MMC phase III is preserved after resection and anastomosis maintaining the amplitude and frequency of small bowel contractions [22]. The small bowel motility index was similar to controls. Nonspecific abnormalities observed in both groups included simultaneous or tonic contractions as well as contractions present in only proximal or distal segments. The duration of phase III after octreotide was also increased in STEP animals [22]. These findings are difficult to reproduce in the clinical setting especially in patients with severe intestinal ischemia or gastroschisis and baseline abnormal motility even before STEP. After STEP, intestinal motility continues to be affected correlating with feeding intolerance and TPN dependency (Fig. 30.2). Thus, preoperative severe dysmotility is a risk factor for poor outcomes from STEP [31].

Intestinal Transplantation

Intestinal transplantation has become an increasingly accepted treatment for children with intestinal failure with 3- and 5-year survival rates of 84 % and 77 %, respectively,

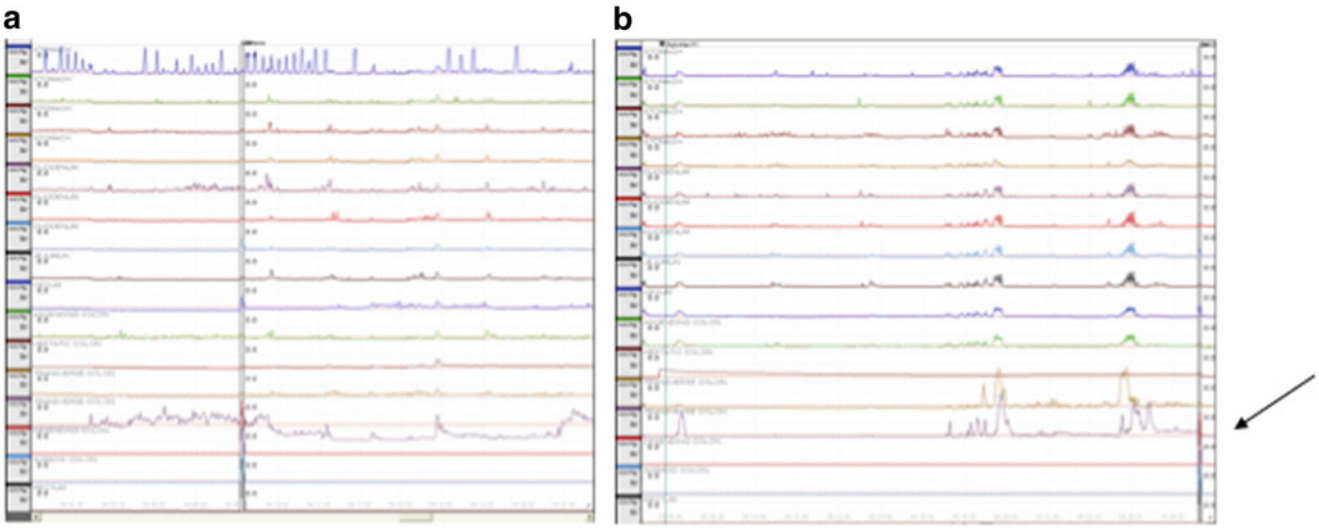

Fig. 30.2 Small bowel and colonic motility in a 4-year-old boy with a medical history of NEC, short bowel syndrome, and post-STEP procedure. (**a**) Presence of simultaneous contractions in the antrum and small bowel in the first eight channels. (**b**) HAPCs in the sigmoid after Bisacodyl stimulation (*arrow*). (Courtesy of Dr. Carlo Di Lorenzo and Dr. Hayat Mousa, Nationwide Children's Hospital, Columbus, OH)

with most patients becoming independent of TPN [32]. The most frequent cause of intestinal failure is short-gut syndrome (SGS) defined by malabsorption, malnutrition, and growth retardation secondary to extensive loss of intestinal length or functional gut mass [33, 34]. Gastroschisis, volvulus, necrotizing enterocolitis, intestinal atresia, chronic intestinal pseudoobstruction, and congenital enteropathy are frequent conditions associated with SGS [32].

Small bowel or multivisceral organ transplantation is often necessary for children after massive intestinal resection including those with less than 25 cm of small bowel without ileocecal valve, congenital intractable mucosal disorders, persistent hyperbilirubinemia, and diminishing venous access, often associated with recurrent episodes of sepsis [35, 36]. The role of performing small bowel motility studies as a gauge to determine whether intestinal transplantation should be undertaken is unclear, but has been proposed as a potential prognostic tool [37]. Most studies have focused on the impact on intestinal motility after transplantation [38].

After intestinal transplantation, maintenance of intestinal motility with coordinated smooth muscle function and adequate absorptive capability is paramount. Animal models have confirmed that intrinsic nerves are generally preserved after transplantation [39, 40]. The consequence of extrinsic denervation from the small bowel may lead to poor functioning of the grafted intestine. In a canine model, for instance, body weight and serum albumin levels remain stable after autotransplantation. However, transplanted animals demonstrated significant defects in fat and D-xylose absorption compared to controls, possibly attributed to overgrowth in fecal flora [39]. In a similar model, dogs undergoing autotransplantation experienced rapid intestinal transit compared to short-gut animals which may suggest that adaptive responses of the transplanted intestine may be impaired by neuromuscular injury associated with denervation or ischemia [41].

Intestinal motility after small bowel transplantation has been studied in children using antroduodenal manometry. Interdigestive phase III motor activity with normal manometric characteristics was seen as early as 3 months posttransplantation in the majority of patients. However, disruption of an orderly MMC was noted across the anastomosis as well as abnormal postprandial motility, which may in part be responsible for abnormal intestinal transit and poor absorption [38]. These studies emphasize how little is known about the effect of small bowel transplantation on motility and underscore the need for future prospective research. Because a significant part of graft motility depends on the Cajal cells, particularly in the context of extrinsic denervation, inflammation of the tunica muscularis either by ischemia reperfusion or by frequent episodes of rejection or infections often leads to poor functioning of the graft and presence of bacterial overgrowth [42]. In animal models, small bowel graft, rejection is associated with decreased MMC phase III amplitude and propagation of contractions [43, 44].

Roux-en-Y Jejunostomy and Bariatric Surgery

Roux-en-Y gastrojejunostomy has been employed in both children and adults for a variety of indications including postgastrectomy for peptic ulcer disease, as a component of bariatric surgery, and for jejunal feeding access [41]. The technique limits reflux of bile into the gastric remnant and esophagus. Common postoperative symptoms attributed to secondary dysmotility include abdominal fullness, distension, pain, nausea, and vomiting [45]. These symptoms are likely the result of interrupted slow-wave electrical conduction which occurs after transecting the jejunum resulting in shortened phase III MMC duration and abnormal motor response to meals [46]. The consequence of disruption of the enteric nervous system may include serious conditions such as ascending cholangitis due to stasis of bowel contents in the proximal limb of the roux segment, known as blind-loop syndrome [47].

It has been shown in both adults and animals that using an "uncut" Roux-en-Y technique may avoid the problems observed with jejunal transection by prolonging the phase III MMC, thereby enhancing digestive clearance [47]. While gastrectomy is uncommon in children, there has been an increase in pediatric gastric surgery to treat obesity particularly in adolescents [48]. Both laparoscopic adjustable gastric banding and laparoscopic Roux-en-Y gastric bypass have been performed in children, but there is a paucity of data examining the effects of these operations on gut motility. Overall, there seems to be an improvement in health-related quality of life based on early studies, which may suggest limited disturbances in motility in these patients [49].

Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia (CDH) is a developmental defect present in less than 1 of 1000 live births resulting in herniation of abdominal viscera into the chest [50, 51]. It is associated with other anatomic malformations in 30 % of the patients resulting in increased mortality [52, 53]. Long-term gastrointestinal problems, most notably refractory gastroesophageal reflux disease (GERD), have been described in patients with prior CDH repair [54]. In a recent multivariate analysis, the incidence of GERD was shown to be 39 % immediately after repair and 16 % 12–18 years after repair. Patients with an intrathoracic stomach and patch closure of the diaphragm seemed to demonstrate the most significant reflux symptoms in the early postoperative period [55].

Reports of intestinal motility disorders in patients with CDH are limited. However, foregut dysmotility has been postulated after CDH repair as evidenced by persistent upper GI symptoms noted in association with abnormal gut fixation seen in nearly 10 % of patients [56]. For example, antral hypomotility with low-amplitude and prolonged phase III contractions has been observed after CDH repair manifesting as symptoms of severe gastroesophageal reflux and delayed gastric emptying scintigraphy testing [57].

Gastroschisis

Gastroschisis is a full-thickness defect in the abdominal wall usually adjacent to the insertion of the umbilical cord with an incidence between 0.4 and 3 per 10,000 births [58]. A variable amount of intestine and abdominal organs may herniate through this defect without the protective covering of the peritoneal sac [59]. Ten percent of infants with gastroschisis develop ischemic injury to the bowel due to vascular insufficiency which may result in intestinal stenosis or atresia [58, 60]. Gastroschisis represents one of the major causes of intestinal failure often necessitating consideration of intestinal transplantation. Approximately 40 % of patients with gastroschisis require parenteral nutrition by the age of 4 months and 10 % by the age of 2 years [61].

Patients with gastroschisis tend to have persistent gut dysmotility with symptoms suggestive of intestinal pseudoobstruction [62]. Even after repair with adequate bowel length, these patients have evidence of profound feeding problems, increased hospitalizations, and mortality [63, 64]. Many of these patients with feeding problems may have neuropathic predominant changes based on antroduodenal manometry (Author RG, unpublished case series). Interestingly, in postnatal autopsy studies, there is no evidence of ganglion cell or generalized myenteric nervous system abnormalities to explain the motility disorders that often accompany cases of gastroschisis [65].

Motility Disorders After Repair of Malrotation and Intestinal Atresia

Malrotation is defined by the absence of midgut rotation before reentering the abdominal cavity during the 12th week of gestation [66]. By this time in embryonic development, the neurons forming the ENS have already migrated from the neural crest to the intestine. Surgical correction (Ladd's procedure) involves division of a fibrous stalk of peritoneal tissue attaching the cecum to the abdominal wall, known as Ladd's bands; widening the small bowel mesentery; appendectomy; and appropriate placement of the colon. Small bowel motility abnormalities including complete absence of motor activity, low-amplitude or slow-frequency contractions, and slow propagation of phase III of the MMCs have been described after performing a Ladd's procedure for these patients [67]. These manometric abnormalities have been associated in some patients with histological changes such as distended neuronal axon hypoganglionosis or vacuolated nerve tracts in the small bowel [68].

Intestinal atresia is a frequent cause of bowel obstruction in neonates. Operative management includes resection of the atresia with primary bowel anastomosis, resection with tapering enteroplasty, temporary ostomy with intestinal resection, enterostomy with web excision, and longitudinal intestinal lengthening procedures. After surgical correction, symptoms of adhesive bowel obstruction occur in close to 25 % of the patients with prolonged adynamic ileus in 9 % and enterostomy prolapse in 2 % [69]. Prolonged small bowel obstruction due to atresia or malrotation can lead to severe refeeding problems in the neonatal period. Cezard et al. described a form of postobstructive enteropathy (POE) of the apparently normal small intestine segment proximal to the obstruction. POE patients showed significant abnormal peristalsis as characterized by barium and carmine transit times. Small bowel manometric recordings are characterized by an absence or abnormal phase III of the migrating motor complex and decreased motility index of the small intestine above the obstruction [70, 71].

Colectomy and Partial Colonic Resection

Colonic resection in children is reserved for chronic conditions such as refractory ulcerative colitis, Crohn's colitis, familial adenomatous polyposis, severe constipation, Hirschsprung's disease, and debilitating motility disorders such as intestinal pseudoobstruction. Small bowel and residual colonic function is contingent on the region and extent of colonic resection as well as the underlying pathology necessitating surgery. As an example, subtotal colectomy is a surgical option to treat severe cases of constipation associated with colonic dilatation. While extensive resection of colon may accomplish reduction in intestinal transit time, it may not eliminate symptoms of pain and bloating suggesting the possibility of a more generalized motor disorder of the gut [72]. Colectomy in these patients may also be associated with uncontrolled diarrhea and fecal incontinence as well as relapsing constipation [73].

The difficulties associated with subtotal colectomy may be due to the adaptive changes in the MMC resulting in increased anaerobic bacterial colonization of the small intestine [74, 75]. Partial colonic resection may alleviate some of symptoms observed after subtotal colectomy particularly if

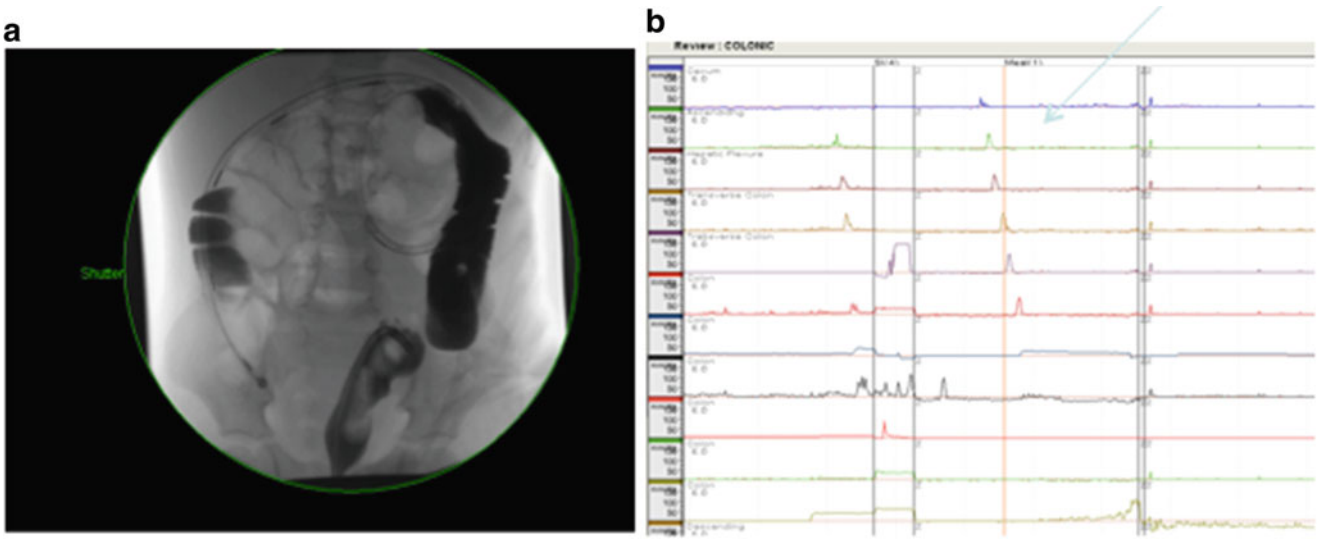

Fig. 30.3 Example of two manometry catheters placed in a retrograde fashion from a colostomy and from the anus. The *top panel* shows the radiology image of the two manometry catheters. The *bottom panel* shows the manometry study. There is evidence of propulsive contractions proximal to a diverting colostomy (top eight channels in the manometry tracing) and absent motility in the distal four channels in the distal colonic segment

performed in conjunction with preoperative motor assessment including Sitz markers, scintigraphy, and antroduodenal and colonic manometry [75–77].

In patients with refractory constipation and colonic dilatation, colonic and antroduodenal manometry may be key diagnostic tests to determine the optimal surgical approach [77–79]. In the absence of demonstrable colonic motility, a decompressive ileostomy or proximal colostomy for several months may allow improvement in the degree of colonic dilatation with return of some degree of motor function in the distal, diverted colon [77, 79]. Performing a subsequent colonic manometry study after a diverting ileostomy or colostomy may allow a more objective surgical decision between ostomy takedown and reanastomosis alone versus reanastomosis combined with partial resection of colon particularly in the context of adequate small bowel motility (Fig. 30.3). A permanent ileostomy may be indicated in the context of persistently absent colonic high-amplitude propagating contractions (HAPCs) particularly in association with abnormal small bowel motility [77].

Summary

The need for small bowel and colonic surgery for a variety of indications is a common occurrence in children. The impact of operative manipulation and interventions on subsequent gut motility may have serious implications in terms of the functional capacity of the remaining intestine to effectively absorb nutrients without gastrointestinal symptoms. Thus, motility testing in children whether performed in the preoperative or postoperative phase of management may play a significant role in the surgical decision-making process. Future studies are needed to better discern the underlying mechanisms responsible for motility problems observed after small intestine and colonic surgery.

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Gastric Function After Fundoplication

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Samuel Nurko

Fundoplication is one of the most common operations performed in children [1–5]. It is a very successful operation to control gastroesophageal reflux, but it can be associated with significant postoperative symptoms that may limit its effectiveness [1–4, 6–8]. The problems and symptoms after fundoplication seem to cluster in two main types: (a) esophageal or (b) gastric [6]. In this chapter we focus mainly on describing gastric function after fundoplication, and therefore on the later symptoms.

Effect on Gastric Sensorimotor Function

Fundoplication reduces the volume of the stomach and uses most of the proximal stomach to create a wrap around the lower part of the esophagus that results in an increase in LES pressure and in the esophagogastric junction contractile integral of 26.3 % [2, 4, 5, 8–10]. The surgery can have a major impact on gastric function, and may explain some of the postoperative symptoms that can be encountered [11]. There have been a few studies that have evaluated gastric accommodation, sensation, and emptying in children and adults after fundoplication. Mousa et al. [5] studied gastric compliance and gastric sensory function before and after Nissen fundoplication in children. They performed barostat studies in 13 children before surgery and repeated the test after surgery in 8. After fundoplication, patients had significantly higher minimal distending pressure values, reduced gastric compliance, and significantly higher pain scores. These indicate that gastric compliance was reduced, and presumably that lead to stimulation of visceral afferents and the heightened perception they noted. Zangen et al. [12] showed that in 12/14 children there was a decrease in gastric volume capacity that produced retching.

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Findings of abnormal gastric accommodation have also been reported in adults. In a case controlled study proximal gastric function was studied with the use of barostat in 12 adult patients that underwent fundoplication and compared with 12 controls [13]. They found that there was no difference between groups in compliance during fasting. However the adaptive relaxation in the fundoplication group was significantly less than that in controls after ingestion of a liquid meal [13]. They also showed that the fundal wrap is not afunctional and is still able to accommodate to pressure increments, that the stomach relaxation after a meal occurs normally, but that in the patients there was a decrease in receptive relaxation. Similar findings related to accommodation were reported by Vu et al. [14] who studied with a barostat 12 adult patients before and after Nissen fundoplication and compared the results with the findings on 12 healthy adults and 12 adults with GERD who did not undergo surgery. The sensation of fullness was increased in the postoperative patients. Again post-Nissen patients had normal compliance, but reduced postprandial gastric accommodation and accelerated gastric emptying.

Other less invasive methods that indirectly assess gastric function have also been used to study gastric function after surgery. By using single photon emission computed tomography with three-dimensional analysis, Bouras et al. [15] showed that patients post-fundoplication had a postprandial/fasting gastric volume ratio that was lower than in healthy controls, again suggesting impaired gastric accommodation. By using the water load test Remes-Troche et al. [16] found that asymptomatic subjects after surgery had higher scores for bloating, nausea, and abdominal pain compared to controls. They found that patients with dyspeptic symptoms after fundoplication had a significantly lower drinking capacity and higher symptoms scores than controls, including patients that were asymptomatic after fundoplication [16]. Their scores were similar than those of patients without surgery and functional dyspepsia, while the scores of asymptomatic fundoplication patients were similar than those of healthy controls [16].

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Visceral hypersensitivity has been associated with abnormal gastric accommodation and hyperalgesia, and cofactors of this hypersensitivity are likely to be wall tension and the function of visceral afferents [17]. Therefore it is possible that patients who do not develop dyspeptic symptoms after fundoplication may have a nearly normal gastric function [16].

The exact mechanism by which these changes in accommodation occur is not clear. There may be alterations in the proximal gastric wall function, the abnormalities may be secondary to vagal dysfunction, or to the mechanical effects of the fundoplication per se [5, 8, 11, 18]. A recent meta-analysis showed that rates of adverse results involving dysphagia, gas-bloat syndrome, inability to belch, and reoperation due to severe dysphagia were significantly higher after laparoscopic Nissen as compared with Toupet fundoplication, suggesting the type of gastric manipulation has an effect on prognosis [1]. The proximal gastric wall seems to work normally as gastric compliance, tone and volume waves have been found to be normal [13, 14]. It is then possible that surgical manipulation itself could impair autonomic pathways affecting the gastric sensorimotor function and that changes in postprandial relaxation after reflux surgery could result from alterations in neurohormonal control [11, 18]. Vagal nerve function after fundoplication has been evaluated by using different methods. By using sham-feeding-stimulated pancreatic polypeptide (PP) test before and after surgery Devault et al. [18] showed that 5/12 with normal testing before the surgery developed evidence of vagal dysfunction after surgery. Interestingly here was no correlation between PP tests and the development or worsening of symptoms after surgery. In another study that evaluated vagal function by seeing PP response to insulin-induced hypoglycemia, Vu et al. found that 11 of their 12 patients responded normally [14]. Given the information described above it appears that the reduced gastric accommodation is probably mechanical in origin [13, 14].

Effects on Gastric Emptying

Patients with GERD frequently have delayed gastric emptying [14]. It has been reported that fundoplication may accelerate gastric emptying for both solids and liquids [13, 14, 19]. More rapid gastric emptying after the creation of a fundoplication is attributed to the loss of accommodation in the stomach, thereby preventing the fundus from expanding to contain the liquid portion of the meal [20]. An acceleration of gastric emptying after Nissen in children has not been consistently found. Mousa et al. [5] found no significant change in emptying for both solids and liquids after surgery, although their patients had normal emptying before the surgery.

A fast gastric emptying after surgery can produce some of the postoperative symptoms that can be encountered [4, 7, 18]. Diarrhea, which can occur in up to 18 % of patients [18], has been correlated with rapid gastric emptying. An exaggerated fast gastric emptying for liquids may produce dumping syndrome [4, 7, 18]. Even though this occurrence is more frequent when a pyloroplasty has been performed, it has been shown to occur also in children and adults in which no pyloroplasty was done. The pathophysiology of dumping syndrome in children is multifactorial, although its incidence and severity appear to be proportional to the rate of emptying [21]. Fonskalrud et al. [3] described a postoperative transient dumping syndrome in 0.9 % of 7467 fundoplications (0–5 %), and in a prospective study of 50 pediatric patients, Samuk et al. [22] reported dumping diagnosed by testing in 30 %. One of the main problems with dumping syndrome is the postprandial hypoglycemia. The mechanisms responsible for that are not fully understood but are thought to involve reduced postprandial gastric relaxation and accelerated emptying, resulting in the precipitous emptying of hyperosmolar, carbohydrate-containing solutions from the stomach into the upper small bowel [3] and subsequent hyperglycemia. Although the occurrence of postprandial hyperglycemia has been blamed for the later hypoglycemia, recent studies have suggested it is most likely related to abnormal glucagon release [23].

Effects on Antroduodenal Motility and Gastric Myoelectrical Activity

The effect of fundoplication on antroduodenal motility has not been clearly established. No prospective studies that have measured antroduodenal motility before and after fundoplication have been reported, but studies of children and adults with postoperative problems have shown abnormal antroduodenal motility [11, 12, 24]. In one study it was shown that 25 of 28 symptomatic children after fundoplication had abnormalities. The most common abnormality found was an absence of the migrating motor complex in 12, while 6 had postprandial hypomotility; other nonspecific abnormalities included clustered, retrograde and tonic contractions [24]. Similar motility abnormalities have been described in adults [11].

In another study of 14 patients with food refusal after fundoplication, an abnormal antroduodenal manometry was found in 9 patients, suggesting that abnormal motility after surgery does not occur in all patients with symptoms. Therefore, it is unclear if the abnormalities were present before the operation or are a result of it. Given that the abnormalities found were similar to those seen in chronic intestinal pseudo-obstruction, and that not all children with problems postoperatively have motility dysfunction, it is likely the abnormalities seen in children probably predated the operation, suggesting that those children had a more generalized

gastrointestinal dysfunction, and not only gastroesophageal reflux. The presence of preoperative gastric myoelectric dysfunction has also been shown. Richards et al. measured gastric myoelectric activity before and after fundoplication with the use of surface electrogastrography in 27 children (17 neurologically impaired and 10 neurologically normal) [25]. They found abnormal gastric electrical activity before surgery in 65 % of the neurologically impaired as compared with 20 % of the neurologically normal group. After surgery an abnormal myoelectrical activity developed in 6 (3 in each group), and in 4 the study deteriorated.

Relation of Postoperative Symptoms to Gastric Dysfunction

It has been reported that up to a third of patients may develop symptoms after fundoplication [5]. The problems and symptoms after fundoplication seem to cluster in two main types: (a) esophageal or (b) gastric [6]. Symptoms commonly seen after antireflux surgery include dysphagia, inability to belch, early satiety, bloating, dyspepsia, gas-bloat syndrome, retching, pain, feeding refusal, diarrhea, and dumping [4, 7, 12, 18]. The cause of dysphagia is multifactorial and can often be corrected with esophageal dilation and occasionally repeated surgery [2, 7]. Loots et al. studied 10 children before and after fundoplication with gastric emptying, and esophageal manometry/impedance studies [2]. They found that peristaltic contractions were unaltered. Complete lower esophageal sphincter relaxations decreased after fundoplication (92 % [76–100 %] vs. 65 % [29–91 %], $P = 0.038$). Four (40 %) patients developed postoperative dysphagia, which was transient in 2. In those patients, preoperative gastric emptying was delayed compared with patients without postoperative dysphagia, 96 min (71–104 min) versus 48 min (26–68 min), $P = 0.032$ [2], again suggesting that abnormal gastric emptying may play a role [2].

The symptom of gas bloat occurs because a compromised ability to eliminate swallowed air by belching, leading to gas accumulation and symptoms of bloating [6]. Inability to belch is an expected outcome after fundoplication and most patients learn to compensate for this symptom [7]. It is commonly assumed that an inability to vent air from the stomach by gastric belching is the cause of the gas-related symptoms that frequently occur after fundoplication [26]. However it has also been suggested that gas-related symptoms are due to excessive air swallowing after fundoplication [27]. It has recently been described that patients who have undergone fundoplication often report that they are still able to belch in the absence of TLESRs and common cavities. Therefore the mechanism of belching may be different after fundoplication and that belches consisted of swallowed air that has been retained in the esophagus due to failed peristalsis [26, 28]. Recently Broeders et al. have demonstrated that in fact most of the postoperative belching is supragastric, and not gastric, an important finding that may have therapeutic implications [26]. The inability to belch gastric contents predisposes to gas-bloat syndrome. Therefore, fundoplication alters the belching pattern by reducing gastric belching (air venting from stomach) and increasing supragastric belching (no air venting from stomach). This explains the increase in belching experienced by some patients after fundoplication, despite the reduction in gastric belching. It can be hypothesized that the reduction in gastric belching incites patients to increase supragastric belching in a futile attempt to vent air from the stomach to reduce postoperative bloating [26].

A recent meta-analysis showed that the overall prevalence of gas-related symptoms was significantly higher after laparoscopic Nissen when compared with laparoscopic Toupet (31.19 % vs. 23.91 %, RR 1.31, 95 % CI [1.05, 1.65], $p = 0.02$). Inability to belch occurred in 33 of 221 (14.93 %) patients following Nissen and 18 of 214 (8.41 %) patients following Toupet, respectively [1]. Booth et al. reported that 18.64 %/10.34 % suffered from gas-bloat symptoms, 62.71 %/63.79 % had postprandial fullness, 74.58 %/67.24 % complained of flatulence, and 25.42 %/31.03 % experienced epigastric pain after both laparoscopic Nissen vs. laparoscopic Toupet [29].

The development of retching, early satiety, diarrhea, pain, and feeding refusal are more difficult to explain [7, 16, 30] and are probably related to the effects that the fundoplication has on sensorimotor gastric function in the absence of a structural or mechanical obstruction [6]. Therefore symptoms after fundoplication are most likely related to the decreased gastric postprandial relaxation, impaired distribution of intragastric food, abnormal gastric motility, visceral hyperalgesia, and to the fact that the ingested material reaches and distends the distal stomach much earlier than physiologically expected [4, 6].

In children Zangen et al. showed a clear relationship between a decrease in gastric volume capacity and retching in children after fundoplication [12]. In adults, Remes-Torche showed with the use of the water load test, that when comparing postoperative patients with or without symptoms, that only those patients with symptoms after fundoplication had visceral hypersensitivity or impaired gastric accommodation or both [16].

There are other factors that may predispose patients to have symptoms. The presence of a fundoplication, which both strengthens the lower esophageal sphincter and decreases transient lower esophageal sphincter relaxations [8, 26, 31], may prevent venting of gas from the proximal stomach and cause increased abdominal distention, particularly when it is known that patients with gastroesophageal reflux swallow large volumes of air routinely [18]. Richards et al. found that children in which there was deteriorating

gastric myoelectrical activity after surgery developed retching postoperatively concluding that in children Nissen fundoplication may be followed by a progression of gastric dysrhythmias that may be associated with retching [25]. In children another prominent symptom after fundoplication can be food refusal which can be secondary not only to gastric dysfunction, but also secondary to pain and behavioral issues [12]. Finally anatomic failure of the fundoplication can play an important role in postoperative symptoms and should always be excluded [6, 8]. Recent studies using MRI fluoroscopy has shown it allows visualization of the normal pattern of hiatal anatomy, as well as for the demonstration of the pathologic pattern of the integrity of a fundoplication wrap and its relationship to the diaphragm [8]. They were able to demonstrate various patterns of fundoplication disruptions that correlated to clinical symptoms [8]. It has the advantage over barium studies that it allows the visualization not only of luminal structures, but the structural details of the esophagus and stomach itself as well as the surrounding structures [8].

Therapeutic Approaches

Given that the symptoms can originate from a variety of underlying problems, it is important to understand the pathophysiology of the symptoms in each patient [12]. Treatment has to then be tailored accordingly, and a multidisciplinary team may be necessary [12]. Drugs that increase gastric accommodation may be tried. Given that $5HT_1$ receptors are involved in gastric accommodation agonists may be used. Drugs like cyproheptadine, sumatriptan, and buspirone have been used [4, 12, 16, 32]. Cyproheptadine, a drug that is widely used in pediatrics to stimulate appetite, is a well-known antagonist of serotonin, histamine H1, and muscarinic receptors, and has been shown to improve retching post-fundoplication [32]. Other drugs that have been used include sumatriptan and buspirone [4, 12, 16]. Prokinetics may be necessary in those children with evidence of delayed gastric emptying. Erythromycin has been used, but can be associated with increase pain [4]. The other prokinetics like metoclopramide, cisapride, and domperidone have limited use given their side effect profile and lack of availability in most parts of the world [4, 7, 12]. The use of botulinum toxin applied to the pylorus can sometimes relieve some of the gas-bloat syndrome symptoms and retching seen postoperatively [33] but controlled trials are necessary. Techniques to decrease the visceral hypersensitivity are usually necessary. Smaller meals, use of anticholinergics and pain modulators (like low dose antidepressants, or gabapentin), and behavioral techniques are often necessary [4, 12]. At times it may be necessary to use jejunal feedings [12].

Summary and Conclusion

Fundoplication may have an impact on gastric sensorimotor function. Fundoplication reduces the volume of the stomach and uses most of the proximal stomach to create a wrap around the lower part of the esophagus. Studies consistently show it may increase the rate of gastric emptying, decrease gastric accommodation, lead to impaired distribution of intragastric food with the ingested material reaching and distending the distal stomach much earlier than physiologically expected, and may also produce visceral hypersensitivity. Postoperative symptoms that may be attributed to gastric sensorimotor dysfunction after surgery include inability to belch, early satiety, bloating, dyspepsia, gas-bloat syndrome, retching, pain, feeding refusal, diarrhea, and dumping. Given that the symptoms can originate from a variety of underlying problems, it is important to understand the pathophysiology of the symptoms in each patient to be able to tailor therapy accordingly.

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Part V

Functional Gastrointestinal Disorders

Rome Criteria for Functional Gastrointestinal Disorders

32

Samuel Nurko and Carlo Di Lorenzo

Background

Functional gastrointestinal disorders (FGIDs) are common condition in children [1–3]. Although they usually represent a benign problem, parents are concerned that the symptoms may be manifestation of a serious disease, the child is often severely disabled and the practitioner may be focused on ordering tests that can diagnose other diseases for which medications or surgeries may be needed [3–5]. It is now well established that pediatric FGIDs are associated with poor quality of life [6] and can have long-term adverse outcomes such as prolonged school absenteeism, depression, anxiety, social phobia, and somatic complaints and may persist into adulthood [3–5]. One of the main challenges in dealing with FGID is that they have no well-established and testable biologic biomarker [7]. Thus, until recently the diagnosis was one of exclusion after multiple tests were performed to be sure there was "no other disease."

In an effort to provide guidance for the recognition of FGIDs in adults, in 1987 a group of experts met in Rome under the leadership of Professor Aldo Torsoli to establish symptom-based criteria to diagnose these conditions [8]. The methodology at that time was mostly based on expert opinion and consensus because the medical literature on FGIDs was sparse at best [8]. In 1991, they published a document aimed at standardizing the evaluation and care of individuals with FGIDs [8, 9]. Initially, 5 committees were created based on anatomical regions: esophageal, gastroduodenal, intestinal, biliary, and anorectal [8, 9]. The reports formed the first Rome symptom-based diagnostic criteria for FGIDs in adult patients. Those initial criteria are now known as the Rome I criteria (in order to keep with the spirit of the location where the meeting took place [8, 9], Rome numerals have since been used to label the iterations of the criteria). The criteria provided clarity and consistency to achieve a clinical diagnosis, made comparisons between groups possible, and opened the door for a new era in the study of FGIDs. Better clinical trials were developed because it was finally possible to enroll in studies more homogenous patient population and the development of new therapeutic agents for FGIDs ensued. As more information and research was generated, it became obvious that the Rome criteria needed to be better defined and validated and the Rome II effort was born [8]. Adult gastroenterologists became enlightened that children, much like adults, suffer from FGIDs and in 1996 a pediatric Rome Committee was formed, in order to address FGIDs in children [8]. This effort was supported by the Rome foundation, and in particular by Dr. Drossman who has been instrumental in his support for the pediatric committees. The initial committee was chaired by Dr. Hyman and cochaired by Dr. Rasquin-Weber, and also included Drs. Hyams, Fleisher, Milla, Staiano, and Cucchiara. The first pediatric criteria were published as part of the Rome II criteria in 1999 [10]. This was the first time that the group proposed a classification system and symptom-based diagnostic criteria for all gastrointestinal syndromes considered to be as manifestation of disordered brain-gut function in the pediatric population [10]. The Rome II pediatric criteria were divided based on symptoms: vomiting, abdominal pain, diarrhea, and defecation disorders. They also took in account the different developmental stages, and emphasis was placed on the child's biopsychosocial context [10]. At the time of the publication of the criteria there was little evidence-based data available, and the criteria were based mostly on the individual experience of the members of the committee. The publication of the Rome II pediatric criteria marked a turning point in the field of FGIDs in children, as it spurred major validation and

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education efforts, as well as clinical studies and trials in pediatrics. Initial efforts to validate the existence of the proposed disorders were undertaken, and validation questionnaires were created [11, 12]. It soon became evident that even though the Rome II criteria represented an important beginning, they needed to be further refined, so the effort to improve them started. When the Rome III effort was born, it was decided to divide the pediatric criteria in two groups, according to the developmental stage of the patients in recognition of the importance that cognition, age, and development have on different phenotypes [13, 14]. Two pediatric committees were formed: (1) neonates and toddlers and (2) children and adolescents. The neonatal and toddler committee was chaired by Dr. Milla and cochaired by Dr. Hyman, and included Drs. Davidson, Fleisher, Benninga, and Taminiau [13]. The Child Adolescent Committee was chaired by Dr. Di Lorenzo and cochaired by Dr. Rasquin-Weber and also included Drs. Forbes, Guiraldes, Hyams, Staiano, and Walker [14]. Care was taken to make sure that members of the committee were diverse in terms of geography, expertise, and gender. The division in two groups may be somewhat arbitrary, given the overlap of some conditions (cyclic vomiting syndrome and functional constipation, for example), but it reflects the fact that the clinical expression of a FGIDs is dependent on an individual's stage of development particularly with regard to physiologic, autonomic, affective, and intellectual development [13, 14]. As the child gains the verbal skills necessary to report pain, it is then possible to diagnose pain-predominant FGIDs. Also, the FGIDs in neonates and toddlers (particularly in the first year of life) have unique characteristics that merit separate description and approach [13]. Finally, given that the decision to seek medical care for a symptom usually arises from a caregiver's concern for the child rather than from the patient himself, effective management depends upon securing a therapeutic alliance with both the caregivers and the children, something that also needs to be individualized based on the age of child [13]. The Rome III criteria continued to greatly advance the field, and a further explosion in the published literature occurred. The criteria were better defined and validated [1, 2, 15–17]. Compared to the Rome II criteria, they were shown to be more inclusive for children with abdominal pain-related FGIDs, and defecation problems [17]. More clinical trials emerged, and the recognition of FGIDs in children improved both at the primary care and at the specialty level. International collaborative studies emerged, and the criteria were validated in different continents [3, 15, 16, 18, 19]. The biopsychosocial model was further embraced and validated and FGIDs disorders in children crossed into well-characterized entities. For the first time, evidence-based treatments and systematic diagnostic approaches were developed [19, 20]. Even though the understanding of the pathophysiology of FGIDs in children remains incomplete, significant progress has been made since Rome III. With new studies validating the criteria and with advances in neurogastroenterology and new therapies, it became necessary to consider another revision of the Rome criteria and the Rome IV committees were created. The same two age-based pediatric committees were kept. The neonate and toddler was chaired by Dr. Nurko and cochaired by Dr. Benninga. Other members of the Committee included Drs. Faure, Hyman, Schechter, and St James Roberts [21]. The Child Adolescent group was chaired by Dr. Di Lorenzo and cochaired by Dr. Hyams and the others members included Drs. Saps, Shulman, Staiano, and van Tilburg [22].

Rome IV Changes

In Rome IV the biopsychosocial model of illness based on the complex interplay of genetic, physiological, psychological, and environmental factors is endorsed and a multidisciplinary approach to evaluation and treatment is emphasized, including psychosocial, pharmacological, and dietary interventions [21, 22]. The era of diagnosing a FGID only when every organic disease has been excluded is waning as we now have sufficient evidence to support symptom-based diagnosis for most conditions [21, 22]. In child/adolescent Rome IV, this concept has been emphasized by removing the dictum that there had to be "no evidence for organic disease" in all FGIDs definitions and replacing it with "after appropriate medical evaluation the symptoms cannot be attributed to another medical condition" [22]. This important change allows the clinician to perform selective or no testing to reach a positive diagnosis of a FGID [22]. We also point out that FGIDs can coexist with other medical conditions that themselves can result in gastrointestinal symptoms (e.g., inflammatory bowel disease) [22]. New sections cover novel FGIDs (such as functional vomiting and functional nausea) and discuss new subgroups of functional dyspepsia and irritable bowel syndrome [22], as well as advances in the understanding of the neurobiology of pain [21]. Rome III "abdominal pain-related functional gastrointestinal disorders" (AP-FGID) has been changed to functional abdominal pain disorders (FAPD) and we have created a new term, "functional abdominal pain—not otherwise specified," to describe children with functional pain who do not fit a specific disorder such as irritable bowel syndrome, functional dyspepsia, or abdominal migraine [22]. Rome IV FGID definitions should enhance clarity for both clinicians and researchers [21]. In the Rome IV document there are also sections on future directions, including the possibility of defining and studying new FGIDs in the future [21]. Among the novelties of Rome IV there are also algorithms for different diagnoses of FGIDs and several clinical vignettes that use the Multi-Dimensional Clinical Profile (MDCP), a tool

which aims at providing a more comprehensive understanding of the issues related to FGIDs in both adults and children. A Rome Pediatric Book that includes all the Rome IV items related to pediatrics has also been completed. The MDCP makes an effort to address also the different pathophysiological mechanisms that may underlie similar phenotypes. Additionally, a Rome Foundation Pediatric Subcommittee on Clinical Trials and the European Medicines Agency (EMA) was created and chaired by Dr. Saps. Other members of the Committee included Drs. van Tilburg, Lavigne, Miranda, Benninga, Taminiau, and Di Lorenzo. Their findings will help to develop patient-reported-outcomes (PRO) and hopefully provide guidelines for the performance of clinical trials in children.

Summary

In summary, we believe that the Rome criteria, although initially being considered mostly a research tool, have now crossed into the realm of clinical relevance. The goal of the criteria is to give caregivers and older patients information, reassurance, and support, and to avoid unnecessary testing. For the provider, they also allow for a positive diagnosis, better research and clinical trials, and consequently better treatment strategies.

Another important question that needs to be addressed is how to prevent FGIDs from becoming a chronic severe debilitating condition and thus decrease their overall impact. Current evidence suggests that the primary care physician and the pediatric gastroenterologist are well positioned to provide effective care, reassure parents, and avoid unnecessary testing [3]. However, we need to recognize there are still tremendous gaps in the knowledge of FGIDs and a lack of uniformity in the approach towards children with FGIDs. Given that prevention may be the best approach for children with FGIDs there is a need for better education and opportunities to improve the management of children with FGIDs in the community. This represents the biggest challenge for the future.

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Infant Regurgitation and Pediatric Gastroesophageal Reflux Disease

33

Yvan Vandenplas

Gastroesophageal reflux (GER) is the involuntary passage of gastric contents into the esophagus and is a completely normal physiologic process [1]. Most reflux episodes are asymptomatic and are of short duration. GER disease (GERD) occurs when GER causes troublesome symptoms and/or complications, by preference confirmed by a health care professional [1]. Although the definition for GERD in children and adults is quite similar, in adults and older children (>11–12 years) it is obvious that GER becomes GERD when the patient himself evaluates the symptoms as troublesome. In younger children (<8 years) and infants, it is the parents (or other caregivers) who interpret symptoms as being troublesome or not. In order to decrease the risk for misinterpretation, it was proposed that a health care professional should confirm that the reflux symptoms are a cause of discomfort and distress to the infant or young child. However, because of the variability of reflux symptoms, there will always be a grey zone between GER and GERD influenced by the subjective interpretation of the child, parent, and health care professionals, as not all patients with GERD develop objective symptoms and signs such as esophagitis. Non-erosive reflux disease (NERD) is likely to be the most frequent presentation of GERD in children also. GERD is associated with an impaired quality of life, which is especially during infancy and early childhood mainly determined by parental perception and coping. Unfortunately, too often a crying and distressed infant is considered as being an infant with GERD.

Spreading information about frequent, common disorders from opinion leaders to the primary health care level is a difficult task. Guidelines on symptoms, diagnosis, and management of GER and GERD were published by the European and North American Societies of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN/NASPGHAN) in 2009 [1]. In 2013 the American Academy of Pediatrics confirmed and approved this document [2]. American family doctors were informed about the existence of these guidelines only in 2014 [3].

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Prevalence

Regurgitation, spitting-up, posseting, and spilling are synonyms and are defined as the passage of refluxed gastric contents into the pharynx, mouth, and sometimes expelled out of the mouth [1]. Regurgitation is distinguished from vomiting by the absence of a central nervous system emetic reflex, retrograde upper intestinal contractions, nausea, and retching. "Vomiting" is defined as expulsion with force of the refluxed gastric contents from the mouth [2, 3]. Vomiting is a coordinated autonomic and voluntary motor response, causing forceful expulsion of gastric contents [1]. Vomiting associated with reflux is likely the result of the stimulation of pharyngeal sensory afferents by refluxed gastric contents. GERD is a spectrum of a disease that can best be defined as manifestations causing esophageal or extra-esophageal troublesome symptoms or esophageal or adjacent organ injury secondary to the reflux of gastric contents into the esophagus or, beyond, into the oral cavity or airways. To be defined as GERD, reflux symptoms must be troublesome to the infant, child, or adolescent and not simply troublesome for the caregiver [4].

Rumination is the voluntary contraction of the abdominal muscles resulting in the habitual regurgitation of recently ingested food that is subsequently spitted up or re-swallowed (see Chap. XX).

Determination of the exact prevalence of GER and GERD at any age is virtually impossible because symptoms are not specific, not all patients seek medical help, many patients are not (fully) investigated, and auto-treatment is frequent. Several epidemiologic studies evaluated the frequency and evolution of infant regurgitation, which is of course only part of the spectrum of GER. Symptoms of acid regurgitation, heartburn, or both occur at least once a week in 10–20 % of adults [5]. About 25 % of infants present with frequent regurgitation [6].

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GER is influenced by genetic, environmental (e.g., diet, smoking), anatomic, hormonal, and neurogenic factors. GER symptoms are associated with an increase in body mass index, waist circumference, and functional constipation [7, 8].

Our group has established 20 years ago normal ranges for pH metry in infants that were hospitalized during 24 h for a polysomnography for sudden infant death screening [9]. At that time, GER was considered as a possible cause for pathological apnea, and it was estimated more ethical to perform the polysomnography and pH metry simultaneous than to prolong the hospitalization for a pH metry in case the polysomnographic recording showed pathologic apneas. However, since then pH probes changed from glass to antimony or ISFET, and it has been shown that these electrodes register different (less reflux episodes) than glass electrodes [10]. For ethical reasons, it is not possible to (re-)do pH probe or multichannel intraluminal impedance (MII) recordings in healthy asymptomatic children.

Pathophysiology

Even today, the pathophysiology of GERD is not fully understood and it is recognized to be a multifactorial disease [11]. Among others, the following factors that have been shown to be involved in the provocation or increase of reflux episodes are sliding hiatus hernia, low lower esophageal sphincter pressure, (inappropriate) transient lower esophageal sphincter relaxation, acid pocket, obesity, prolonged esophageal clearance, and delayed gastric emptying [11]. Multiple mechanisms influence the perception of GER symptoms, such as the acidity of the refluxate, its proximal extent, the presence of gas in the refluxate, longitudinal muscle contraction, mucosal integrity, and peripheral and central sensitization. Three major lines of defense limit the degree of GER and GERD: the anatomical "antireflux barrier," consisting of the LES and the diaphragmatic pinchcock and angle of His, the esophageal peristalsis and clearance, and the esophageal mucosal resistance [12].

Interindividual variation of reflux perception suggests different esophageal sensitive thresholds, which is in part determined by capsaicin levels and vanilloid receptor-1 play [13]. There are acid, temperature, and volume sensitive receptors in the esophageal mucosa. Gene expression scores may facilitate the differential diagnosis between reflux and eosinophilic esophagitis. Genes may also help to determine the risk for Barrett esophagitis and adenocarcinoma [14]. Esophageal sensitivity to acid decreases when esophagitis has healed. Duodenal fat increases the sensitivity to reflux.

New information about pathophysiology is mainly restricted to adults. Acidity of the refluxate may also relate to a localized proximal gastric area called "the gastric acid pocket" that may persist even in the postprandial period when (the rest of the) stomach content is neutralized by the meal [15]. Although this entity has been fairly well documented in adults, data in children are scarce. Delayed gastric emptying has been documented in (a proportion of) infants and children with symptomatic GER, in particular in those with neurologic disorders [12]. We could not find a relation between gastric emptying and MII/pH results in children with cystic fibrosis [16]. Position and sleep influence GER and gastric emptying. In the recumbent position noxious gastric materials, rather than air, are positioned at the cardia and may more easily move into the esophagus, especially when the LES tone is decreased during sleep. Both salivation and swallowing are markedly reduced during sleep, further impairing clearance.

Symptoms of GERD

While reflux occurs physiologically at all ages, there is at all ages also a continuum between physiologic GER and GERD. The spectrum of GER(D) symptoms in infants and children varies with age. Possible associations exist between GERD and hiccups, chronic cough, chest pain, hoarseness, recurrent otitis media, asthma, pneumonia, bronchiectasis, ALTE (acute life-threatening event), laryngotracheitis, sinusitis, and dental erosion, but causality or temporal association were not established [17] (Table 33.1). The paucity of studies, small sample sizes, and varying disease definitions do not

Table 33.1 Symptoms and signs that may be associated with gastroesophageal reflux

Symptoms
Recurrent regurgitation with/without vomiting
Weight loss or poor weight gain
Irritability in infants
Ruminative behavior
Heartburn or chest pain
Hematemesis
Dysphagia, odynophagia
Wheezing
Stridor
Cough
Hoarseness
Signs
Esophagitis
Esophageal stricture
Barrett's esophagus
Laryngeal/pharyngeal inflammation
Recurrent pneumonia
Anemia
Dental erosion
Feeding refusal
Dystonic neck posturing (Sandifer syndrome)
Apnea spells
Apparent life-threatening events (ALTE)

allow to draw firm conclusions [17]. During recent years, no further evidence has been accumulated on these topics.

Uncomplicated Regurgitation

Excessive regurgitation is one of the symptoms of GERD, but the terms regurgitation and GERD should not be used as synonyms [4]. While regurgitation (spilling, spitting up, posseting) is a typical GER symptom in infants, it is seldom in older children and adults. According to a recent review, about 25 % of infants present with regurgitation severe enough for parents to seek medical help, which can be limited to reassurance, e.g., by providing information on the natural evolution and adjusting feeding volume and frequency [1, 2, 18]. Regurgitation that persists after the age of 6 months strongly decreases during a 3-month follow-up with conservative treatment [19]. A prospective follow-up reports disappearance of regurgitation in all subjects before 12 months, although the prevalence of feeding refusal, duration of meals, parental feeding-related distress, and impaired quality of life was observed, was higher in those who presented with regurgitation (even after disappearance of symptoms) compared to those who never regurgitated [20].

Irritability or infant distress may accompany regurgitation and vomiting. However, in the absence of other warning symptoms, it is not an indication for extensive testing [1]. Parental coping-capacity or anxiousness will determine if a physician is contacted or not. Regurgitation is frequent in infants because of the frequent feedings, large liquid volume intake, the limited capacity of the esophagus (10 mL in newborn infants), the horizontal position of infants, etc. Infants ingest per kg bodyweight more than twice the volume that adults do (100–150 mL/kg/day compared to 30–50 mL/kg/day) causing more gastric distention and as a consequence more TLESRs.

Recurrent and Persistent Regurgitation/ Vomiting

Although usually regurgitation causes little more than a nuisance, important regurgitation may (seldom) result in caloric insufficiency and malnutrition. Poor weight gain is a crucial warning sign that necessitates clinical management, but it occurs seldom in otherwise healthy infants with GER, and necessitates clinical management (Table 33.2). These infants need a complete diagnostic workup. Hospitalization is often needed. There may be abnormal sucking and swallowing. These infants have no apparent malformations, and may be diagnosed as suffering "non-organic failure to thrive" ("NOFTT"), a "disorder" that sometimes is attributed to social/sensory deprivation, socioeconomic or primary maternal-child problems. Poor weight gain, feeding refusal, back-arching, irritability, and sleep disturbances have been reported to be related as well as unrelated to GERD [1, 2, 21].

Table 33.2 Warning signals requiring investigation in infants with regurgitation or vomiting

Bilious vomiting
GI bleeding
– Hematemesis
– Hematochezia
Consistently forceful vomiting
Onset of vomiting after 6 months of life
Failure to thrive
Diarrhea
Constipation
Fever
Lethargy
Hepatosplenomegaly
Bulging fontanelle
Macro/microcephaly
Seizures
Abdominal tenderness or distension
Documented or suspected genetic/metabolic syndrome

GER(D) and Cow's Milk Protein Allergy (CMPA)

The symptoms of CMPA overlap with many symptoms of GER, or may coexist or complicate GERD [26]. An association between GER and cow milk "hypersensitivity" was observed in infants and children with severe GER(D) [22]. Esophageal impedance showed that the incidence of nonacid postprandial reflux was decreased after a feeding with an amino acid-based formula compared to standard cow milk-based infant formula [23]. However, this may as well be related to CMPA as to a more rapid gastric emptying. An extensive hydrolysate was shown to reduce esophageal acid exposure in preterm infants with feeding intolerance and reflux symptoms [24]. We showed that a non-thickened or thickened extensive hydrolysate were equally effective in infants presenting with frequent regurgitation and with a positive cow's milk challenge test [25]. However, in infants included in the same study but with a negative challenge test, the thickened hydrolysate was more effective in obtaining a reduction of episodes of regurgitation compared to the non-thickened hydrolysate [25].

GER(D) and Distressed Behavior

GERD occurs much less frequent than regurgitation in infants; therefore, anti-reflux medication is not often needed [1, 2, 18]. The same amount of distress and crying may be evaluated by some parents as easily acceptable while it will be

unbearable for other parents. There is substantial individual variability and some healthy infants may cry up to 6 h a day. In infants, crying, irritability, sleep disturbance, and "colicky symptoms" have long been considered as heartburn equivalents. Irritability may accompany regurgitation and vomiting; however, in the absence of other warning symptoms, irritability and distress are not an indication for extensive testing or for treatment of GERD [1, 18]. The duration of crying is not related with the severity of acid reflux [21]. A meta-analysis concluded that proton pump inhibitors do not decrease crying and distressed behavior in infants [26]. Many factors, such as colic, constipation, CMPA, and neurologic disorders, among many others, may cause infant irritability and GER(D) in a subgroup of infants. There is substantial individual variability and some healthy infants may cry up to 6 h a day.

In adults, "non-erosive reflux disease" ("NERD") is a general accepted entity. Again in adults, impaired quality of life, notably regarding pain, mental health, and social function, has been demonstrated in patients with GERD, regardless of the presence of esophagitis [27]. The developing nervous system of infants seems susceptible to pain (hyper-)sensitivity when in contact with acid despite the absence of tissue damage. Some adults "learn to live with their symptoms" (only half of the heartburn complainers seek medical help, although 60 % takes medications) and acquire tolerance to long-lasting symptoms. A relation between GER, GERD, and feeding refusal has not been established in infants. There is no evidence that routine acid-suppressive therapy is effective in infants who present only with distress and irritability.

GER(D) and Heartburn

Heartburn is the predominant GER symptom in adults, occurring weekly in 15–20 % and daily in 5–10 % of subjects. While the verbal child can communicate pain, descriptions of the intensity, location, and severity may be unreliable until the age of at least 8 years, and sometimes later [4].

GERD and Esophagitis

Esophagitis is defined as visible breaks of the esophageal mucosa [1]. Histology is recommended to rule out complications such as Barrett esophagus or other causes of esophagitis such as eosinophilic esophagitis. Differences in patient recruitment, availability of endoscopy, definition of esophagitis, and self-treatment make it virtually impossible to estimate the incidence of esophagitis.

Odynophagia usually represents esophageal inflammation. Children with GER symptoms present esophagitis in 15 up to 62 %, Barrett's esophagus in 0.1–3 %, and refractory GERD requiring surgery in 6–13 % [1, 28]. Erosive esophagitis in 0–17-year-old children with GERD-symptoms was reported to be 12.4 %, and increasing with age [29]. The median age of the group with erosive esophagitis was 12.7 ± 4.9 years, versus 10.0 ± 5.1 years in those without erosive esophagitis [29]. The incidence of erosive esophagitis was only 5.5 % in those younger than 1 year [29]. But, of course, patient selection and recruitment, differences in definition of esophagitis, and availability of self-treatment determine these data.

In nonverbal infants, behaviors suggesting esophagitis include crying, irritability, sleep disturbance, and "colic." However, while the incidence of infantile colic is about 20 % [6], the incidence of esophagitis at this age is only 5 % [29, 30]. As a consequence, infant crying is not an indication for acid-reducing treatment. Infants may also appear very hungry until their first swallows and then become irritable and refuse to drink.

Dysphagia is linked to a stricture or esophagitis, both eosinophilic and reflux-related. Eosinophilic esophagitis (EoE) is a chronic immune-/antigen-mediated esophageal inflammatory disease associated with esophageal dysfunction resulting from severe eosinophil-predominant inflammation. The reasons for the impressive rise in the prevalence of EoE are still poorly understood. Atopic features, allergic symptoms, or positive allergic tests are reported in more than 90 % and peripheral eosinophilia in 50 % of patients although these findings depend on patient selection. A genome-wide association study on 351 patients with EoE identified the 5q22 locus encoding TSLP and WDR36 as an EoE susceptibility locus [31]. However, environmental factors may be more relevant than genetic susceptibility [32]. At endoscopy, a pale, granular, furrowed, and occasional ringed esophageal mucosa and, in more severe cases, esophageal stenosis may even appear [1]. But the esophageal mucosa may also appear visually normal, what highlights the importance of histology. The hallmark of EoE is an eosinophilic infiltrate of >15 eosinophils per high power field (HPF) whereas, in reflux esophagitis, the eosinophils are in general limited to less than 5/per HPF. Similarly to reflux esophagitis there is no specific symptom of EoE but dysphagia for solids is often reported in older children, while symptoms in infants are more reflux-like including vomiting, regurgitation, feeding refusal, and failure to thrive [33]. The overlap between GERD and EoE is well recognized and failure of PPI treatment is a prerequisite to diagnose EoE [33].

In reflux esophagitis, the distal and lower eosinophilic infiltrate is in theory limited to less than 5 per high power field (HPF) with 85 % positive response to GER treatment, compared to primary EoE with >20 eosinophils per HPF. Demonstration of failure of PPI treatment as a condition needed to diagnose EoE brought reflux esophagitis back in the picture [33, 34].

GER(D) and Extra-Esophageal Manifestations

Many extra-esophageal manifestations such as asthma, pneumonia, bronchiectasis, ALTE (apparent life-threatening event), laryngotracheitis, and sinusitis are reported to be associated with GER. However, the paucity of studies, small sample sizes, and varying disease definitions did not allow to draw firm conclusions [17]. Different pathophysiologic mechanisms are direct aspiration, vagal-mediated bronchial and laryngeal spasm, and neural-mediated inflammation.

Asthma

Chronic pulmonary hyperinflation favors many GER mechanisms. An association between asthma and reflux has been reported [17]. Wheezing appears more related to GERD if it is nocturnal. There are no data that help in selecting patients in whom reflux treatment may result in a reduction of asthma medication [1, 17]. In one study in a small series of 46 children with persistent moderate asthma, 59 % had an abnormal pH metry and reflux treatment resulted in these in a significant reduction of asthma medication [35].

Another study found omeprazole ineffective in improving asthma symptoms and parameters [36]. Once more, patient selection is of crucial importance.

Cough

GERD is not a common primary cause of chronic cough in children [37]. In children with reflux-related cough, baseline impedance levels have no role in identifying reflux-induced esophageal mucosal ultrastructural changes [38]. Reflux burden, symptom association, and rates of esophageal pathology were determined in children with intractable cough and wheezing: 58 % had abnormal reflux testing (67 % had an abnormal MII-pH test and 32 % had abnormal esophageal biopsies) [39]. The most common MII-pH abnormality was an abnormal symptom association between cough and reflux and the most common endoscopic abnormality was reflux esophagitis. Seven percent of patients presenting only with cough were diagnosed with eosinophilic esophagitis [39]. Both acid and nonacid or weakly acid GER may precede cough in children with unexplained cough, but cough does not induce GER [40]. In children with reflux-related cough, dilated intercellular space diameter appears to be an objective and useful marker of esophageal mucosal injury regardless of acid exposure, and its evaluation should be considered for those patients where the diagnosis is uncertain.

ENT Manifestations

Several studies revealed the presence of pepsin in middle-ear fluid, albeit with a huge variation in incidence (14–73 %) [1, 41]. Also bile acids have been detected in middle-ear liquid, in higher concentrations than in serum [42]. The exact meaning of these findings remains unclear as there are no randomized controlled intervention trials. About one-third of children that have pepsin in their middle-ear fluid are reported to have abnormal MII-pH investigations [43]. Pepsin and pepsinogen in middle-ear effusion are probably caused by laryngo-pharyngeal reflux and may be involved in the pathogenesis of otitis media [44]. However, little is known about the esophageal reflux symptoms these children do or do not present, the results of reflux tests in those without pepsin in the middle-ear fluid, the long-term outcome, and the impact of reflux therapy. A proof of cause and effect between extra-esophageal reflux and middle-ear inflammation is still missing [45].

GER(D) and Apnea, ALTE, and SIDS

Literature can best be summarized as follows: series fail most of the time to show a temporal association between GER and pathologic apnea, apparent life-threatening events (ALTE), and bradycardia [1]. However, a relation between GER and short, physiologic apnea has been shown [46, 47]. Selected case reports or small series have been published showing that exceptionally that pathologic apnea can occur as a consequence of GER.

GER(D) and Dental Erosions

The hypothesis that there is a widely prevalent association between dental erosion and atypical GERD is gaining more support [48]. Acid, rather than nonacid reflux, seems to have a significant role in the pathogenesis of tooth erosion [49].

Juice drinking, bulimia, and racial and genetic factors that affect dental enamel and saliva might be confounding variables that have been insufficiently considered [1]. There are no long-term (intervention) follow-up studies in high-risk populations.

GER(D) and 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.

GER(D) and Cystic fibrosis

Patients with cystic fibrosis (CF) have a high prevalence of acid GER, even before respiratory symptoms develop [50]. GER(D) is more frequent in patients with CF than in the general population, and also more frequent than in patients with other chronic lung diseases [51]. Increased GER measured with pH metry or MII-pH recording has been reported with a range between 19 and 100 % in infants and children [51]. Acid reflux is more prevalent than nonacid reflux in children with CF [52]. In CF patients, GER is also increased in patients without reflux symptoms [53]. GER is a primary phenomenon and is not secondary to cough [54]. Patients with CF and increased reflux have more severe lung disease [55].

Increased bile acids in saliva and sputum of patients suggest aspiration of duodenogastric contents [54]. The aspiration of bile acids is associated with increased airway inflammation [54].

GER is in CF patients as well as in all other patients mainly treated with acid suppressants, with proton pump inhibitors inducing the most effective acid suppression. However, the potential adverse effects of acid suppression need to be balanced against the benefits of the therapy. Ranitidine and PPI have been shown to improve the efficacy of the pancreatic enzymes with consequent enhancement of digestive compensation [56, 57]. PPI are mainly initiated as treatment for classic esophageal GER symptoms, or extra-esophageal symptoms such as chronic cough and other respiratory symptoms belived to be caused by GER, or - in patients with cystic fibrosis - to improve the efficacy of pancreatic enzymes [51]. PPI reduce acid GER but do not affect nonacid GER or increase even nonacid GER [58]. Although other literature suggests that PPI may also reduce nonacid reflux as it reduces gastric secretion. The effects of PPI on respiratory parameters are contradictory. Patients receiving PPI have been reported to have a significantly smaller yearly decline of maximal expiratory flow [59]. However, others reported that patients receiving PPI showed a trend to earlier and more frequent pulmonary exacerbations [60]. Chronic PPI treatment may result in a paradoxically increased inflammatory effect in the airways [61] (side effects of PPI: see treatment).

GER(D) and Neurologic Impairment

Neurologically impaired children accumulate many risk factors for severe GERD: spasticity or hypotonicity, supine position, constipation, etc. (see Chap. XX). Diagnosis of reflux disease in these children is often difficult because of their underlying conditions. Whether this group of patients has more severe reflux disease, or has less effective defense mechanisms, or presents with more severe symptoms because of the inability to express and/or recognize symptoms at an earlier course of the condition remains open for debate. Response to treatment, both medical and surgical, is poor in the neurologically impaired child compared to the neurologic normal child.

GER(D) and Other Risk Groups

Children with congenital abnormalities or after major thoracic or abdominal surgery are at risk for developing severe GERD. Children with anatomic abnormalities such as hiatal hernia, repaired esophageal atresia, and malrotation have frequently severe GERD [62]. Gastroesophageal problems in children born with esophageal atresia are common (see Chap. XXX). Routine follow-up with endoscopy and pH metry in esophageal atresia patients is warranted [63]. GERD in these children is often refractory to medical treatment and requires antireflux surgery. However, the high rates of wrap failure invite close follow-up in all cases and reoperation or other measures whenever necessary [64].

Although there is abundant literature on overweight and increased GER in adults, data in children are scarce. There are no data in literature that preterm babies have more (severe) reflux than term born babies, although many preterm babies are treated for reflux. The role of reflux in patients with bronchopulmonary dysplasia and other chronic respiratory disorders is not clear.

GERD and Complications

Severe complications of GERD such as Barrett's esophagus and esophageal adenocarcinoma are seldom in otherwise healthy children. If these severe complications are found, they occur mainly in "at-risk" populations such as esophageal atresia and neurologically handicapped children. Barrett's esophagus is a premalignant condition in which metaplastic specialized columnar epithelium with goblet cells is present in the tubular esophagus. Differences in esophageal mucosal resistance and genetic factors may partially explain the diversity of lesions and symptoms. In a series including 402 children with GERD without neurological or congenital anomalies, no case of Barrett's esophagus was detected [28]. In another series including 103 children with long-lasting GERD, and not previously treated with H_2 receptor antagonists (H_2RAs) or a proton pump inhibitors (PPIs), Barrett's esophagus was detected in 13 %. Reflux symptoms during childhood were not different in adults without than in adults with Barrett's esophagus [65]. Barrett's esophagus has a male predominance, and increases with age. Patients with short segments of columnar-lined esophagus and intestinal metaplasia have similar esophageal acid exposure but significantly higher frequency of abnormal bilirubin exposure and longer median duration of reflux symptoms than patients without intestinal metaplasia [66]. There is a genetic predisposition in families in patients with Barrett's esophagus and esophageal carcinoma [1].

Peptic ulcer and esophageal and gastric neoplastic changes in children are extremely seldom. In adults, a decreased prevalence of gastric cancer and peptic ulcer with an opposite increase of esophageal adenocarcinoma and GERD has been noted over the last 30 years [67]. This has been attributed to independent factors amongst which are changes in dietary habits such as a higher fat intake, an increased incidence of obesity, and a decreased incidence of *Helicobacter pylori* infection [67]. Among adults with long-standing and severe reflux the odds ratios are 43.5 for esophageal adenocarcinoma and 4.4 for adenocarcinoma at the cardia [68]. It is unknown whether mild esophagitis or GER symptoms persisting from childhood is related to an increased risk for severe complications in adults.

Diagnosis

Diagnostic procedures are not discussed in detail. History in children is difficult and considered poorly reliable up to the age of minimally 8 or even 12 years old [1]. History is still "the first and most important thing to do" but it is obvious that history has also its limitations. A GER questionnaire score or "response to PPI" does not accurately diagnose GERD [69]. Orenstein developed the "infant GER-questionnaire" [70], intended to result in an objective, validated, and repeatable quantification of symptoms suggestive for GERD. The I-GER was revised (the "I-GERQ-R") in 185 patients and 93 controls, resulting in an internal consistency and test-re-test reliability of over 0.85 [71]. However, Aggarwal and coworkers obtained with the same I-GER-Q a sensitivity of only 43 % and a specificity of 79 % [72]. Moreover, pH metry results were not different according to a "positive" or "negative" score of the I-GER-Q [72]. Vandenplas and coworkers showed that not one question was found to be significantly predictive for the presence of esophagitis. The I-GERQ cutoff score failed to identify 26 % of infants with GERD (according to pH metry results or presence of esophagitis) and was positive in 81 % of infants with a normal esophageal histology and normal pH metry results [73]. Deal et al. developed two different questionnaires, one for infants and one for older children, and showed that the score was higher in symptomatic than in asymptomatic children [74]. In other words: the correlation between questionnaires and results of reflux investigations is poor.

Barium contrast radiography, nuclear scintiscanning, and ultrasound are techniques evaluating postprandial reflux. Normal ranges have not been established for any of these procedures. There is broad consensus that barium studies are not recommended as first-line investigation to diagnose GER(D), although it is in many centers the only diagnostic technique available.

Modern endoscopes are so miniaturized that scope preterm infants of less than 1000 g has become technically easy. There is a poor correlation between the severity of symptoms and presence and absence of esophagitis. In children with reflux-related cough, dilated intercellular space diameter appears to be an objective and useful marker of esophageal mucosal injury regardless of acid exposure, and its evaluation should be considered for those patients where the diagnosis is uncertain [23]. Biopsies of duodenal, gastric, and esophageal mucosa are mandatory to exclude other diseases [1]. Histology is also necessary to distinguish reflux from eosinophilic esophagitis.

Manometry does not demonstrate reflux, but is of interest to analyze pathophysiologic mechanisms causing the reflux, mainly by visualizing and measuring TLESRs, and is indicated in the diagnosis of specific conditions such as achalasia [1].

Esophageal pH metry remains the best method to measure acid in the esophagus, but not all reflux causing symptoms is acid and not all acid reflux is causing symptoms (see Chap. XX). While the Bravo-capsule is popular in the USA, it is hardly used in other parts of the world. Although normal ranges have been established for pH metry, they are nowadays of limited value since these are hard- and software dependent [11]. The demonstration of a time-association between GER episodes and symptoms is one of the major indications for this technique, which has in fact been poorly used for pH metry.

Multiple intraluminal impedance (MII) measures electrical potential differences (see Chap. XX). As a consequence, the detection of reflux with MII is not pH dependent, but in combination with pH metry it allows detection of acid (pH < 4.0), nonacid or weakly acid (pH 4.0–7.0), and alkaline reflux (pH > 7.0). It also measures the esophageal height of the refluxate. The optimal time frame to be considered as "time-association" and the optimal parameter to calculate a significant association are still debated. Interestingly, pH-only episodes, reflux episodes detected with pH metry but not with MII (drop in pH without bolus movement), occur relatively frequent [75]. pH-only events occur mainly during the night and in young infants. A good correlation between manual and automated analysis of MII baselines was found [76]. Distal compared to proximal esophageal MII baselines were significantly lower in children with a positive overall pH-MII outcome [77]. During the last 3–5 years, interest has focused on baseline impedance which was shown to be lower in esophagitis, and treatment of esophagitis with PPI does increase baseline impedance [78]. Baseline impedance is reported to be age dependent, what is likely to be related with the size of the esophagus [79, 80]. Moreover, since esophagitis does decrease the baseline, and since the definition of an impedance reflux is a decrease of impedance with >50 %, severe esophagitis may have a normalizing effect on interpretation of MII tracings. If the baseline is already very low, there will be fewer episodes in which the impedance still decreases with >50 %. MII-pH monitoring does increase the sensitivity to diagnose GERD; however, when used alone, it results in poor specificity in patients without acid-suppressive therapy [69].

Each GER investigation technique measures different aspects of reflux. Therefore, it is not unexpected that the correlation between the results of the different techniques is poor. There is no "always-best" investigation technique. Endoscopy is the only diagnostic tool to identify esophagitis; 24-h pH metry measures acid GER and MII detects all GER episodes.

Treatment Options

The labeling of an otherwise healthy infant as having a "disease" increases parents' interest in medicating unnecessarily their infant [81]. The use of disease labels may promote overtreatment

Table 33.3 Schematic therapeutic approach

Phase 1	Parental reassurance. Observation. Life-style changes. Exclude overfeeding
Phase 2	Dietary treatment (decrease regurgitation)
	Thickened formula, thickening agents, extensive hydrolysates or amino acid based formula in cow's milk allergy
	Positional treatment (°)
Phase 3	For immediate symptom relief: Alginates (some efficacy in moderate GERD); Antacids only in older children
Phase 4	Proton pump inhibitors (drug of choice in severe GERD; more safety data needed)
	H_2 receptor antagonists less effective than PPIs
Phase 5	Prokinetics (but not one product available on the market in 2015 has been shown to be effective)
	Would treat pathophysiologic mechanism of GERD
Phase 6	Laparoscopic surgery
Efficacy and safety data in infants and children for most anti-GER medication is limited	
(°): data on 40° supine sleeping position in infants are limited	

by causing people to believe that ineffective medications with adverse effects are both useful and necessary [81].

Therapeutic options start with reassurance, followed by nutritional management and positional adaptations, and medication (mainly acid reducing) to end with surgery. Therapeutic intervention should always be a balance between intended improvement of symptoms and risk for side effects (Table 33.3).

Nonintervention

There are no data to suggest that early intervention during infancy would change the course GER(D) later in life, mainly because it has not been studied. Recent accumulation of data suggests a decreased quality of life in a number of parents of infants presenting with frequent regurgitation, even if the regurgitation has disappeared [20]. Although symptoms improved in more than half of the infants with reflux esophagitis followed longitudinally for 1 year without pharmacotherapy, histology remained abnormal in all [82]. It is not known if treatment of GER during infancy changes the outcome in adults. If treatment is prescribed, not only efficacy, but also side effects of the treatment should be taken into account.

Regurgitation: Thickened Feeding

The most common reason to seek medical help for parents with young infants with reflux symptoms is frequent troublesome regurgitation and infant distress. Non-pharmacologic treatment (reassurance, dietary and positional treatment) is recommended as an appropriate first approach. Parental coping determines whether regurgitation and infant distress are considered as troublesome or not. Reassurance while showing compassion for the impaired quality of life is of importance [1, 2, 83, 84]. Data suggest that parental reports during a first consultation may be inaccurate and overestimate the incidence of regurgitation [84], similar to what is well known regarding crying infants or infant colic. Therefore, a "prospective 3-day diary" may help in bringing reassurance. Regurgitation is not a reason to stop breastfeeding. Observation of feeding and handling of the child during and after feedings is mandatory. Many infants are overfed or fed with an inappropriate technique [1]. Reassurance showing comprehension for the impaired quality of life is of importance [1].

Thickened formula or Anti-regurgitation formula reduce the frequency and severity of infant regurgitation, and are therefore recommended as an enforcement tool to reassurance. Thickened formula reduces regurgitation more and faster than happens naturally. Commercialized thickened formula is preferred to thickening agents added to formula at home; the nutritional content of the thickening agent and its effect on osmolality has been considered in the commercialized formula [1]. Cow milk allergy may be a cause of reflux, regurgitation, and vomiting, often accompanied by distressed behavior [1, 2].

Positional Treatment

In GERD patients, TLESRs, GER, distension of proximal stomach, and gastric emptying are increased in right lateral compared to left lateral position [1, 85]. Sleeping positions to decrease regurgitation and GER is the strategy of right lateral positioning for the first postprandial hour with a position change to the left thereafter to promote gastric emptying and reduce liquid GER in the late postprandial period [85, 86]. However, there is a significantly increased risk of SID in the side compared to the supine sleeping position [87]. In preterm infants left side position decreases GER [88]. The results of a pilot-study with the "Multicare-AR Bed®" suggest that a special bed that nurses the infant in a 40° supine body position reduces regurgitation, acid reflux (measured with pH monitoring), and reflux-associated symptoms (evaluated with the I-GERQ) [89].

(Alginate-)Antacids and Mucosaprotectors

Alginate(-antacids) have mainly been validated in adults. No new pediatric studies have been published. The key therapeutic advantage of antacids is their rapid onset of action, within minutes. Results showed a marginal but significant difference between Gaviscon Infant and placebo in average

reflux height (being better for placebo !), and raises questions regarding any perceived clinical benefit of its use [90]. Data on compliance in infants and children (these products have a poor taste) and side effects (many antacids have a high aluminum content) are missing. A recent study suggesting that magnesium alginate plus simethicone is more effective than thickened feeding needs confirmation [91].

Extrapolation from adult data makes it unlikely that mucosaprotectors would be effective in children.

Anti-Acid Medications

Since proton pump inhibitors (PPIs) are more effective in acid suppression than H^2 receptor antagonists (H^2RAs), PPIs are considered the preferred option for treatment of (acid) GERD in children and adults. If the microgranules are enteric coated, the capsules can be opened and administered orally or via a feeding tube, in suspension in an acidic medium such as fruit juice, yogurt, or apple sauce. A "home-made" liquid formulation, produced by dissolving the granula, not the microgranula, in 8.4 % bicarbonate solution is an effective way to administer PPI to infants [1]. Ranitidine is still used in infants because there is no liquid PPI commercially available in most countries, and the pharmacy-made liquid PPI has a limited duration of stability. It has been shown in adults and children that PPI do not reduce the incidence of reflux episodes [58]; they only change the pH of the reflux from acid to nonacid or weakly acid. Omeprazole is approved in the USA and Europe for use in children older than 1 year of age; in the USA, lansoprazole is approved as well. Esomeprazole is approved in the USA for short-term treatment of GERD with erosive esophagitis in infants aged from 1 to 12 months [92]. In Europe, approval for esomeprazole is identical to the approval of omeprazole. Lansoprazole, omeprazole, and pantoprazole are metabolized by a genetically polymorphic enzyme, CYP2C19, absent in approximately 3 % of Caucasians and 20 % of Asians. Salivary secretion is decreased with omeprazole (and increased with cisapride).

Anti-acid medications are among the most commonly prescribed medications in many neonatal intensive care units to treat clinical signs considered to be caused by GER, such as apnea, bradycardia, or feeding intolerance, despite the lack of evidence of efficacy in this population and for these symptoms [93–95]. The concept that infant irritability and sleep disturbances are manifestations of GER is largely extrapolated from adult descriptions of heartburn and sleep disturbances that improve with antacid therapy [1]. PPI have been shown to not reduce infant crying and irritability.

Although PPIs are generally well tolerated, interest has focused on potential adverse events. Prolonged treatment of pediatric patients with PPIs has not caused cancer or significant histological abnormalities. There are different categories of adverse effects related to PPI such as idiosyncratic reactions, drug–drug interactions, drug-induced hypergastrinemia, and drug-induced hypochlorhydria [1]. Idiosyncratic reactions such as headache, diarrhea, constipation, and nausea occur in up to 12–14 % of children taking PPIs [1]. Acid suppression or hypochlorhydria causes abnormal gastrointestinal microbiota and small bowel bacterial overgrowth in up to 25 % of all children [83]. The prevalence of infectious respiratory and gastrointestinal tract infections is increased in patients on chronic PPI treatment [1]. PPIs, particularly if administered for >30 days or in a high dose, showed an association with community acquired pneumonia [96]. Hypomagnesemia is reported as a rare but severe complication [97]. Whether or not PPI are associated with an impairment of bone mineralization remains open for debate [98]. Gastric acid suppression may predispose patients to develop food allergy [99]. Anti-acid medication during pregnancy was reported to increase the risk to develop asthma in the offspring [99, 100].

Prokinetics and Other Medications

From the pathophysiologic point of view, prokinetic drugs are the most logic therapeutic approach to treat non-erosive reflux disease in infants since acid plays only a minor role in GERD in this age group. According to the NASPGHAN-ESPGHAN guidelines, the adverse events of prokinetics outweigh the potential benefit, since the latter was never clearly demonstrated [1]. Prucalopride has received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) on the European Marketing Authorisation Application (MAA) for the treatment of chronic constipation in adults, but has been withdrawn for pediatric use.

Bethanechol, a direct cholinergic agonist, is studied in a few controlled trials and has uncertain efficacy and a high incidence of side effects in children with GERD.

Baclofen, 4-amino-3-(-chlorophenyl)-butanoic acid, is a gamma-aminobutyric acid (GABA)-B receptor agonist, used to reduce spasticity in neurologically impaired patients. Baclofen was shown to reduce the number of TLSERs and acid GER during a 2 h test period and to accelerate gastric emptying [101]. Out of 53 patients (mean age 6.1 years), taking PPI once (53 %) or twice daily (47 %) at the time of initiation of baclofen, 35 (66 %) patients experienced a significant reduction in clinical symptoms at their first follow-up visit [102]. In the remaining 18 patients, however, baclofen was stopped because of either no response ($n = 15$) or adverse events ($n = 3$) [102]. The data on baclofen are still very limited and the number of adverse events do not support widespread use. A baclofen seemed initially a more promising molecule, but failed as well.

Surgery and Therapeutic Endoscopic Procedures

Most of the literature on surgical therapy in children with GERD consists of retrospective case series in which documentation of the diagnosis of GERD and details of previous medical therapy are deficient, making it difficult to assess the indications for and responses to surgery [1]. Adult series report that between 37 and 62 % are taking PPI a few years after the intervention [103, 104]. Different surgical approaches do exist. In general, experience seems to be the best guidance for choosing the preferred technique. While antireflux surgery in certain groups of children may be of considerable benefit, a failure rate of up to 22 % has been reported [1]. Children with underlying conditions predisposing to the most severe GERD comprise a large percentage of many surgical series. Different anti-reflux surgical approaches do exist. In general, experience seems to be the best guidance for choosing the preferred technique. Therapeutic endoscopic procedures are rarely indicated and should only be performed in units where there is evidence of experience.

The transoral incisionless fundoplication procedure can complement the current surgically and medically available options for children with GERD, especially in complicated patients such as those with neurological impairment [105]. Surgery is indicated when symptoms are life-threatening or when a child beyond the age of 2–3 years is depending on chronic treatment with anti-acid medications.

Total esophagogastric dissociation is an operative procedure that is useful in selected children with neurologic impairment or other conditions causing life-threatening aspiration during oral feedings.

The Future

Significant changes in the diagnosis and management of GER and GERD in infants and children are not expected in the next 5 years. Epidemiologic data should bring an answer to the question if early intervention in infants with troublesome regurgitation does have an impact on later outcome. Better insights may be accumulated on the frequency and long-term prognosis of symptoms categorized as functional gastrointestinal disorder. The initial enthusiasm about the contribution of impedance to the diagnosis of GER(D) has tempered. As long as an effective, safe, and nonacid reducing medication has not come on the market, the clinical impact to study nonacid or weakly acid reflux is limited. Prospective trials in patients with extra-esophageal manifestations are needed to clarify the causal role of GER in these patients. Pediatric data on the role of the "gastric acid pocket" are still missing.

Guidelines and recommendations are needed in special interest groups, such as patients with esophageal atresia, cystic fibrosis, and neurologically handicapped children. The conflicting results of acid-inhibiting medication in cystic fibrosis patients, decreasing acid reflux, improving nutritional outcome but also increasing gastrointestinal and respiratory infections need further studies.

For the majority of GERD patients that are otherwise healthy, no major changes are to be expected. However, tools should be developed to better spread the news: guidelines and recommendations do hardly reach primary health care. An App ("GiDi-App") has been developed to help primary care health providers with the diagnosis and management of functional gastrointestinal disorders in infants. The App is free available of Google-Play and Apple-Store.

Conclusion

The incidence of GER in healthy infants and children is unknown since it is unethical to investigate asymptomatic children. Regurgitation is a common condition in infants. GERD is a multifactorial disease, independent of age. There is a wide spectrum of symptoms and signs both for GER and GERD, which are partially age dependent. Infant regurgitation spontaneously disappears with increasing age. Regurgitation in infants is frequent cause of parental anxiety. Since "time is the cure," reassurance is the cornerstone of its management. Although regurgitation is not a reason to stop breastfeeding, thickened formula does reduce regurgitation and contributes to reassure parents. Isolated infant crying and/or distress without the presence of other symptoms is not a symptom of GERD. More in infants than in older children, there is an overlap between symptoms of eosinophilic esophagitis, cow's milk protein allergy, and GERD. Esophageal and extra-esophageal symptoms and signs caused by reflux do exist, although the evidence for causal relation between reflux and extra-esophageal manifestations is difficult to predict in an individual patient. At-risk populations such as patients with severe neurological disorders, cystic fibrosis, and esophageal atresia have been identified. There is no best standard diagnostic technique. The value of validated questionnaires for the diagnosis and follow-up has been demonstrated. The best investigation to diagnose esophagitis is endoscopy with biopsies. In children with extra-esophageal reflux symptoms, pH metry and MII-pH recording are the recommended techniques. Multiple intraluminal impedance combined with pH monitoring has not yet become a standard diagnostic technique because it is expensive, time consuming, and the additional information provided is limited. Treatment of regurgitation and moderate reflux disease should focus on reassurance, dietary and possibly also positional treatment. Alginates are useful when immediate symptom relief is required, although there are almost no

data in children. Medical therapeutic options are mainly limited to acid-secretion reducing medications, although not all reflux symptoms and disease are caused by acid reflux. The best medical treatment of acid GERD are proton pump inhibitors. Attention focused on potential adverse effects, mostly related to an altered gastrointestinal microbiome because of the decreased gastric acidity. Laparoscopic surgery is recommended in patients dependent on chronic anti-acid treatment and in those with severe, sometimes even life-threatening symptoms.

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Infant Colic

34

Valerie Sung and Ian St James-Roberts

Aims

This chapter examines the origins and current understanding of infant colic. The evidence about gastrointestinal (GI) disturbance as a cause of colic is reviewed in detail after summarising other approaches. The chapter aims to support clinical practice and to advance research.

Origins of the Term 'Infant Colic'

The word 'colic' originates from the ancient Greek word 'kolikos', which means crampy pain and shares its root with the word 'colon' [1]. GI dysfunction leading to discomfort or pain has traditionally been considered to underlie infant colic [2–4]. This idea can be traced back at least to Thomas Phaire's 1544 *Boke of Chyldren* [5], often considered the first English language paediatric textbook, which included '*Colyke and Rumblyng in the Guttes*' as a common childhood ailment. More recently, the eminent English paediatrician, Ronald Illingworth, referred to '*three month colic*' as crying which was probably caused by '*a localised obstruction to the passage of gas in the colon*' [2] and as '*pain that is obviously intestinal in origin*' [6].

Another early milestone was Wasz-Höckert and colleagues' work that introduced the idea of cry 'types', such as hunger, anger and pain cries, which were presumed to allow a listener to use the cry's sound to identify the cause of the crying [7]. This supported the idea that infant pain cries could be distinguished and tied to gastrointestinal dysfunction.

A further key publication, Morris Wessel and colleagues' 1954 study, marked a turning point by recognising that infant colic is primarily about crying behaviour. Their widely cited 'Rule of Threes' defined 'a fussy or colicky infant' as: '*one who*, *otherwise healthy and well fed*, *had paroxysms of irritability*, *fussing or crying lasting for a total of more than three hours a day and occurring on more than three days in any one week*' [8]. This progression from inferred causation to observable behaviour was also apparent in the approach adopted by the influential Rome Foundation of expert gastroenterologists, whose Rome III criteria for colic stipulated that colic crying had to start and stop suddenly and occur for 3 or more hours/day for at least 3 days in a week [9].

Much of the research which followed set out to explore the assumptions involved in these early reports. The studies can be grouped into three strands: Developmental; Clinical Impact and Organic (including GI) Causes. We will examine these in turn.

Emergence of a Developmental Explanation for Unexplained Crying in Early Infancy

Does the Crying of Infants with Colic Sound Atypical or Distinguish Pain?

Audio recordings of crying periods that parents identified as colic bouts were compared to hunger and other crying bouts of the same or other infants, using trained listeners and acoustic analyses. Although some studies reported differences [10, 11], these were small, inconsistent across studies and confounded by other factors, while the most exhaustive study of this kind found no evidence that colic cries sounded distinct [12, 13]. Nor did the colic crying bouts identified by parents start suddenly. Typically, they were part of long periods of normal, relatively intense, fussing and crying more generally. These findings coincided with a careful

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review of the 'cry type' evidence [14] which questioned the assumption that crying behaviour maps directly onto, and so identifies, its cause. Instead of discrete cry types, such as hunger, anger and pain cries, the authors concluded that crying in young babies is a *graded signal*, which conveys information about the degree of an infant's distress, but not what is causing it. Parents work out the causes of crying through experience: e.g. crying 4 h after feeding is likely to be a hunger cry. The graded signal viewpoint has since been widely adopted.

'Unsoothability' of Infant Crying as a Source of Parental Distress

Instead of an abnormal sound, the features of crying in early infancy found to distress parents most were the unexplained, prolonged and 'unsoothable' nature of the crying bouts involved [15–17]. This 'unsoothability' was not confined to parent reports: trained researchers using an established soothing protocol were also unable to stop the crying [17], indicating that it was an objective characteristic of the infant's crying. Rather than the amount of crying highlighted by the Rule of Threes, the unsoothable bouts were the chief source of parents' concerns because these made the crying uncontrollable for them [16, 17]. Studies in both Canada and the USA found that 'unsoothable crying'—and particularly the maximum bout length of unsoothable crying—was more strongly associated with caregiver frustration than amount of daily crying [16].

The Infant Crying Peak

The idea that prolonged infant crying is due to a clinical disturbance in a minority of infants was challenged by studies of infants in the general community, which found peaks in crying at around 1–2 months of age in a variety of countries [18–20]. This peak in crying amount was accompanied by increased crying in the afternoon and evenings and long and unsoothable crying bouts [15, 17, 21]. All three features declined by 5 months of age and the infants' subsequent development was normal [22, 23]. Together with similar findings in other mammalian species and evidence that prematurely born babies cry most at a similar maturational age, the crying peak has been interpreted as a universal of early infancy [24]. That is, these early crying features are linked to normal developmental processes and occur more or less in infants generally in the first 4 months of age [25].

This developmental view of the origins of unexplained crying in most 1–4-month-old infants has been widely accepted, including by the Rome Foundation handbook on Functional GI disorders [9, 26]. It has important implications for clinical practice which will be considered in the next section. However, it is important to acknowledge its limitations. It does not readily account for the evening clustering, explain why some infants fuss and cry so much more than others at this age, or identify the developmental mechanisms involved. One hypothesis is that the crying is due to the maturational reorganisation of brain systems that normally occurs at around 2 months of age as reflex mechanisms are replaced by systems involving cortical control of behaviour [24, 27, 28]. The long and unsoothable crying bouts are attributed to a temporary loss in neurological control of behaviour during this transition, so that infants respond quickly and strongly, or cannot stop crying once it has started [29, 30]. The implication is to move the search for causation from the gut to the central nervous system. However, this hypothesis remains speculative and there is little direct evidence to support it so far. A more detailed review is available elsewhere [31].

The Clinical Impact of Prolonged Infant Crying

Although many parents are worried by prolonged crying in a young baby, not all seek clinical help, highlighting the importance of parental complaint, rather than infant crying, as the basis for health service provision and costs. The finding that first-time parents were more likely to seek help, although first babies do not cry more than later-borns [20, 32] led to evidence that parental individual and cultural factors need to be considered alongside infant crying. For instance, parents who view the crying as a sign their baby is still hungry are likely to terminate breastfeeding prematurely [33] or overfeed [34], while the crying can trigger parental distress and depression [35–37], poor parent–child relationships [38], problems with long-term child development [39], and infant abuse in a small number of cases [40, 41].

For clinicians and health services, these findings point to the need for cost-effective methods for identifying and supporting parents of infants who cry a lot, rather than focusing solely on infant crying. Two promising initiatives are the inclusion of protocols for supporting such parents in the Rome IV guidelines for gastroenterologists [26] and the growth of evidence that community programmes can increase parental knowledge of crying and the factors that precipitate 'shaken baby syndrome' (SBS) [42, 43]. Whether these interventions can reduce the incidence of SBS in the same way the 'back to sleep' campaign reduced SIDS (Sudden Infant Death Syndrome) is unknown, but there is provisional evidence that these programmes can be effective [40, 44, 45].

Table 34.1 gives definitions for infant colic for clinical and research purposes which recognise the importance of parental as well as infant parts of the clinical picture. The more stringent criteria for clinical research purposes are designed to

Table 34.1 The Rome foundation diagnostic criteria for infant colic, 4th Edition

For Clinical purposes must include all of the following
1. An infant who is less than 5 months of age when the symptoms start and stop
2. Recurrent and prolonged periods of infant crying, fussing or irritability reported by caregivers that occur without obvious cause and cannot be prevented or resolved by caregivers
3. No evidence of infant failure to thrive, fever or illness
'Fussing' refers to intermittent distressed vocalisation and has been defined as 'behaviour that is not quite crying but not awake and content either'. Infants often fluctuate between crying and fussing, so that they are difficult to distinguish in practice
The Committee also decided that for Clinical Research purposes, to diagnose infant colic the child must meet the clinical criteria PLUS both of the following
1. Caregiver reports infant has cried or fussed for 3 or more hours/day during 3 or more days in 7 days in a telephone or face-to-face screening interview with a researcher or clinician
2. Total 24-h crying plus fussing in the selected group of infants is confirmed to be 3 h or more when measured by at least one, prospectively-kept, 24-h behaviour diary

From Nurko S, Benninga M, Faure C, Hyman P, Schechter M, St James-Roberts I. Childhood functional gastrointestinal disorders: neonate/toddler. In: Drossman DA, Chang L, Chey WD, Kellow J, Tack J, et al. eds. *Rome IV*: *The Functional Gastrointestinal Disorders*, *edn. IV*. Raleigh, NC: The Rome Foundation.; 2016, with permission

enhance uniformity of studies to help isolate the infant factors involved. The recent Rome IV guidelines propose methods for measuring infant crying and provide normative figures for crying amounts [26]. Asking parents to measure their baby's crying and comparing the results to normative figures should provide reassurance in many cases.

Organic Causes

Incidence of Organic Cases

Alongside the evidence that most infants who cry a lot in early infancy are healthy and developing normally, a small but important minority have been found to have organic disturbances. For example, two reviews concluded that up to 10 % of infants taken to clinicians because of prolonged crying have an organic disturbance [46, 47]. A study of all the infants who were presented to a Canadian paediatric hospital because of crying or irritability over a period of 1 year found that 12 of 237 (5.1 %) had a serious underlying organic aetiology [48].

Detection and Management of Cases Involving Organic Disturbance

In managing a crying infant, an important first step is to exclude and treat any organic causes that may contribute to the crying. Routine clinical observations and history taking

Table 34.2 'Red flags' for identifying cases where prolonged infant crying may be due to organic disease proposed by an international expert panel

Extreme or high pitched cry
Lack of a diurnal rhythm
Symptoms after 4 months of age
Frequent regurgitation, vomiting, diarrhoea, blood or mucus in stools, feeding difficulties, weight loss
Maternal drug ingestion
Abnormal physical examination

Modified from Gormally S. Clinical clues to organic etiologies in infants with colic. In: Barr RG, St James-Roberts I, Keefe MR (eds.), *New Evidence on Unexplained Early Infant Crying*: *Its Origins*, *Nature and Management*. Skillman, NJ: Johnson & Johnson Pediatric Institute; 2001:133–148, with permission

are often sufficient for this purpose: for instance in the Canadian hospital series described above, most cases with organic disturbance were visibly unwell. Since most definitions of infant colic exclude cases involving fever, illness or failure to thrive, cases with an organic aetiology in the first 4 months may be best described as 'colic-like'. Alternatively, the word colic may be avoided entirely and should not be used with infants over 4 months of age (Table 34.1) [26].

Although there are no universally agreed protocols for identifying organic cases, several expert groups have proposed draft versions. Table 34.2 lists the 'Red Flags' for this purpose developed by an international expert group [25] and Fig. 34.1 provides a more detailed workup. An important proviso is that the sensitivity and specificity of these schemes are unknown. Critical evaluation in clinical practice and research should lead to refinement and increase their effectiveness.

Research into Specific GI Causes and Dietary Management Options for Infant Crying

Food Allergy

Food allergy, particularly cow's milk protein allergy, is widely regarded as the most common organic deficit causing prolonged infant crying [49, 50]. Although the incidence is unknown, one estimate is that 2 % of infants overall are food allergic [49]. It is unclear how many such infants cry a lot. Cow's milk protein allergy probably accounts for less than 5 % of cases of colic [51], and should be considered if the infant has other symptoms such as bloody or mucousy diarrhoea, failure to thrive, poor feeding, significant vomiting, eczema and family history of atopy [52, 53]. In such cases, a limited trial of hypoallergenic formula, or maternal cow's milk protein elimination diet in exclusively breastfed infants is recommended.

However, the use of hypoallergenic formula or excluding dairy from the mother's diet cannot be recommended for all infants with colic. The reasons are threefold. First, maternal

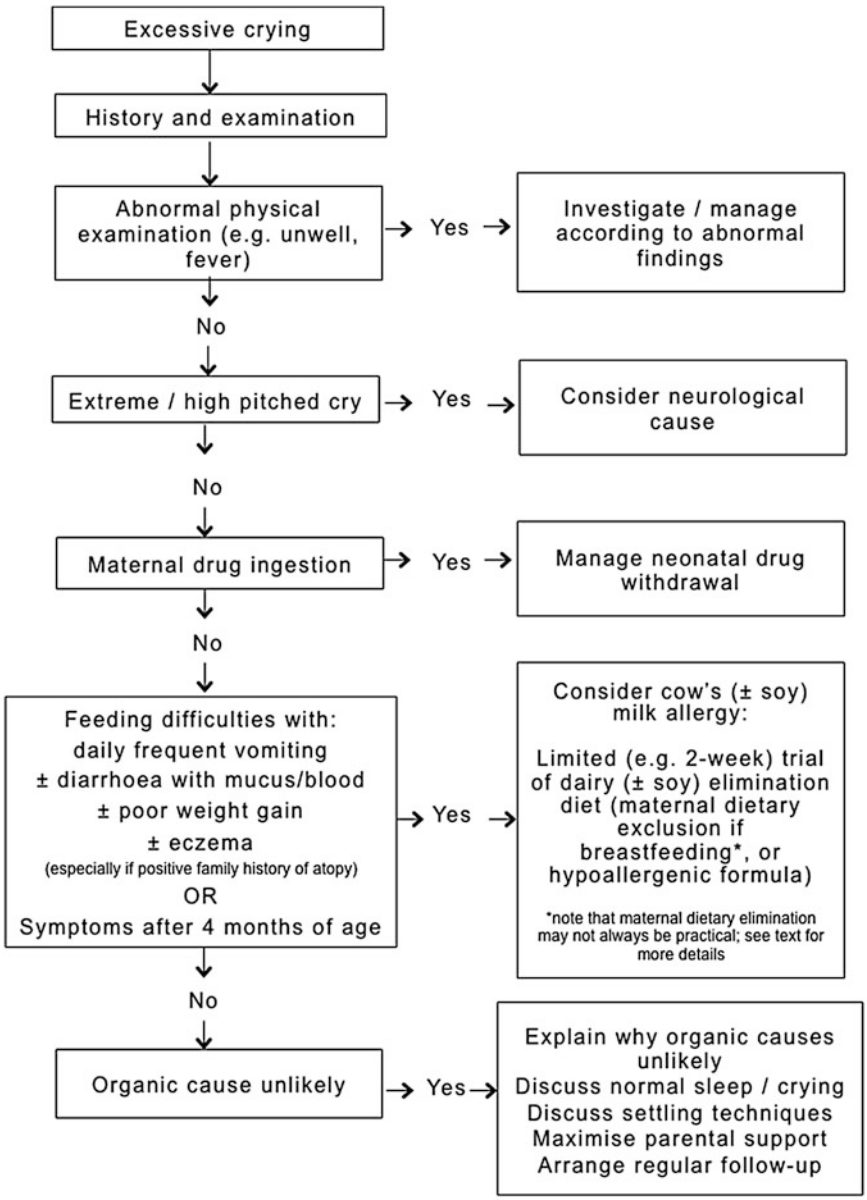

Fig. 34.1 Algorithm for workup of a crying infant

hypoallergenic diets are difficult to follow and maintain. Second, only a minority of infants with colic respond to cow's milk protein elimination [49, 54]. Third, the evidence for their use in infant colic is not conclusive. Although at least six randomised trials have suggested extensively hydrolysed formulae—that is, cow's milk-based formula with the proteins broken down by enzymes—to be effective in managing infant colic [3, 55–59], and only two trials have indicated them to be ineffective [60, 61], all trials have methodological limitations. Many were not blinded [55, 59] or inadequately blinded [56, 60], used inappropriate comparators (e.g. dietary modification versus medication [55], a hydrolysed formula versus another hydrolysed formula [57]), were biased by crossover effects [55], or included infants who may not have had true colic [58]. The majority of studies did not clearly describe the method of generating random allocation sequence or the process of randomisation. The effectiveness of partially hydrolysed formulae is more controversial, with one unblinded trial showing effectiveness [62] and the other not [63]. Two studies suggested a completely hydrolysed formula (that is, amino acid-based formula) to be effective, but both had small sample sizes and neither were randomised trials [64, 65]. Studies examining the elimination of cow's milk protein from the breastfeeding mother's diet have also yielded contradictory results, with four indicating effectiveness [56, 60, 66, 67] and two not [55, 68]. Two systematic reviews in 2012 concluded that there was evidence to suggest hydrolysed formulae to be beneficial to infants with colic; however, most of the studies had methodological inconsistencies and biases. They concluded

that the role of maternal hypoallergenic diets in breastfed infants was less clear [69, 70].

Soy formula has been shown in one randomised trial to be effective [71], with two other poor quality trials supporting this [55, 72]. However, the methodological flaws of the latter two trials mean the results cannot be conclusive. One trial used dicyclomine hydrochloride rather than a true placebo as the comparator [55]. The other was a small trial of 19 infants, and the study was possibly biased by crossover effects [72]. One other trial found soy formula to be just as effective as partially hydrolysed formula, without comparing them to a cow's milk-based formula [63]. Without a proper placebo for comparison, the results cannot be conclusive. In addition, soy formula is no longer recommended for infants less than 6 months old due to inconclusive evidence that it may cause harm to young infants (through excessive phytoestrogen compounds) [73].

Colonic Gas, Hyperperistalsis and Gut Hormones

Excessive intragastrointestinal air, or colonic gas, has often been proposed as a cause of infant colic. However, little evidence has come forward to support this theory. In 1969, Harley et al. demonstrated radiographically normal gastric outlines during colic episodes [74]. Measures to prevent aerophagia are ineffective in preventing colic [75], and the use of gas-reducing agents such as simethicone are also conclusively ineffective [76, 77]. Moreover, intragastrointestinal gas could be a result of swallowed air from crying—that is, an effect, and not a cause [78].

Early authors proposed that colonic hyperperistalsis, spasms or increased rectal pressure could underlie colic [79]. This is based on the evidence that dicyclomine hydrochloride, an agent that may relax colonic smooth muscle and reduce spasms, is effective in treating colic [80–84]. This drug, however, has significant, potentially life-threatening side effects, and therefore is no longer recommended for use in infants. A trial of a herbal tea containing an antispasmodic was also effective [85], but the mixture was associated with possible carcinogenic effects and therefore not recommended [86]. These findings do, however, provide evidence that gut spasms may contribute to colic in some infants. The gut hormones motilin and ghrelin, both stimulators of gastric motility, have been found to be higher in infants with colic compared to controls [87, 88]. Whether these findings have practical applications is not yet clear.

Carbohydrate Malabsorption/Lactose Overload

Many authors have suggested carbohydrate malabsorption, lactose overload or lactase insufficiency as causes for infant colic. The excess carbohydrates, such as lactose, in the gut may cause bloating and discomfort. Excess lactose could be a result of lactase insufficiency or lactose overload from excessive consumption of, for example, lactose-rich human foremilk. However, there is insufficient evidence for this as a cause of colic [51]. Studies examining breath hydrogen levels (a by-product of lactose malabsorption) [89–92] and the use of lactase supplementation or lactose elimination have yielded conflicting results [49, 93–96]. The evidence for lactose explanations of colic is weak. Other dietary changes, such as altering the concentrations of fibre [97] and carbohydrates in formulae [98], are ineffective in infants with colic.

Gastro-oesophageal Reflux Disease

Gastro-oesophageal reflux disease (GORD) is one of the most debated aetiologies of infant colic. Gastro-oesophageal reflux (GOR) is defined as the physiological passage of gastric contents into the oesophagus with or without regurgitation and vomiting [99]. GORD, also termed 'pathological reflux', is present when reflux of gastric contents causes troublesome symptoms or complications [99], such as oesophagitis and failure to thrive [100]. In infants, there is no symptom or symptom complex that is diagnostic of GORD or predicts response to therapy [99]. GOR, GORD and 'reflux' are labels often given interchangeably to infants with colic.

There is widespread belief in the community that GOR/GORD plays a major role in infant colic. At the same time, health professionals extensively prescribe anti-reflux medications to infants with colic. However, the evidence for the role of GOR/GORD is lacking. Studies have failed to demonstrate any association between GOR/GORD and crying in infants [100, 101]. In a study of 151 hospitalised infants with excessive crying, 60 % of whom were less than 3 months old, all infants underwent oesophageal pH monitoring. Crying and fussing duration did not correlate with the number of reflux episodes or the fractional reflux time, both measures of GORD [101]. GORD was associated with frequent vomiting more than five times per day, and feeding difficulties only [101]. The study authors stated that in the absence of frequent overt regurgitation, significant GORD was unlikely, implying that 'silent reflux'—that is, reflux without vomiting—was an unlikely cause of infant crying. These results are congruent with those from a previous retrospective review of irritable infants who underwent pH monitoring [100]. In contrast, another smaller study of 27 hospitalised infants with colic who all underwent oesophageal pH monitoring found 61.5 % to have GORD [102]. However, most of these infants were more than 3 months old, and the study did not define GORD by fractional reflux time.

Not only is the link between crying and GOR/GORD unclear, but four randomised trials have consistently concluded that anti-reflux medications are ineffective for crying [103–106]. This is not surprising, given that systematic reviews have concluded that anti-reflux medications are ineffective in improving *all* GOR symptoms, including crying

[107, 108]. Considering the possibility of their associated adverse effects such as increased risk of infections and later osteoporosis [108–110], anti-reflux medications should not be used in managing infants with crying.

Gut Microbiota and the Role of Probiotics

Gut Microbiota

The role of gut microbiota in infant colic has recently been under intense scrutiny. The first study that examined this in 1994 found no significant differences in gut microbiota between infants with and without colic, except for *Clostridium difficile* (*C. difficile*) which more frequently colonised infants with colic during the time of peak crying when compared to controls [111]. *C. difficile* is a bacterium known to cause antibiotic-associated diarrhoea.

Over the last 10 years, an Italian group has documented in four separate cross-sectional studies ($n = 56$–87) that breastfed infants with colic have different gut microbiota compared to breastfed infants without colic. However, these differences have not been consistent. In their 2004 study, breastfed infants with colic were less frequently colonised by *Lactobacillus* species than those without colic [112]. Yet, in another study the following year, breastfed infants with and without colic had similar overall colonisation rates but different patterns of *Lactobacillus* species—*Lactobacillus brevis* and *Lactobacillus lactis lactis* colonised only those with colic, while *Lactobacillus acidophilus* colonised only those without colic [113]. The infants with colic were also more likely to have a family history of atopy [113]. This could be a significant confounder, considering that a study in 2010 suggested that infants with cow's milk protein allergy have higher gut concentrations of anaerobic and *Lactobacillus* species, and lower gut concentrations of *Bifidobacteria*, when compared with non-allergic controls [114]. In 2009, the Italian group suggested breastfed infants with colic had more gas-forming coliforms and *E. coli* concentrations than those without colic [115]. The group's 2011 study replicated these findings, and suggested that two out of 27 *Lactobacillus* strains tested had an antimicrobial effect against six gas-forming coliform species isolated from breastfed infants with colic [116]. This finding is interestingly congruent with the group's 2004 study showing less *Lactobacillus* species in infants with colic compared to those without [112], further supporting the notion that infants with colic may have more gas-forming coliform species that contribute to gaseous distension and subsequent distress.

Other studies have also suggested a role of gut microbiota in infant colic. In a 2008 Finnish study of 18 breastfed infants with and without colic, those with colic had higher prevalence of indole-producing coliforms, such as *Escherichia* and *Klebsiella* species [117]. In a 2009 study of 36 infants with and without colic, those with colic had lower microbial diversity and greater levels of *Klebsiella* species, while the control group had *Enterobacter* and *Pantoea* species that were not detected in the group with colic [118]. A 2012 Finnish study of 89 healthy infants without colic who were at risk of developing allergies suggested *Bifidobacterium* and *Lactobacillus* species to be protective against crying and fussing in the first 3 months of life [119]. A 2013 Iranian study of 70 breastfed infants with and without colic found *Lactobacillus acidophilus* to be present in 20 % of infants without colic, but absent in those with colic [120].

Two recent studies have implicated *Helicobacter pylori* (*H. pylori*) in infant colic. A 2012 Saudi Arabian study of 85 infants with and without colic found a higher proportion of infants with colic had positive *H. pylori* stool antigen compared to those without colic [121], and similar results were found in a 2013 Egyptian study of 100 infants with and without colic [122]. This finding is interesting considering *H. pylori* is an organism known to cause chronic gastric inflammation [123, 124], and is a well-known cause of gastritis in adults. However, *H. pylori* colonisation is often asymptomatic. It may be associated with short-term abdominal pain lasting less than 3 months, but not chronic recurrent abdominal pain in children [125]. There is conflicting evidence for its association with epigastric pain in children [125]. In addition, the prevalence of *H. pylori* infection in children, although not extensively described, is believed to be very low and, therefore, its role in infants is uncertain. The prevalence of *H. pylori* in children and adolescents in Europe and North America is less than 10 % [126]. In a study of children in Chile, the prevalence of *H. pylori* was as low as 1 % at 3 months of age, rapidly increasing after 15 months of age to 20 % at 24 months of age—an age by which colic has well and truly resolved [127].

Probiotics

The most exciting recent development in the search of an effective dietary strategy to manage infant colic is the use of probiotics. Probiotics are 'live micro-organisms which, when administered in adequate amounts, confer a health benefit on the host' [128, 129]. Probiotics may affect infant crying by altering gut microbiota, leading to changes in gut-mediated pain perception, gut motility, mucosal layers and gut permeability, reduction in gut inflammation and inhibition of gut bacteria. One particular strain of probiotic, *Lactobacillus reuteri*, has been shown to be effective in reducing infant crying in four randomised trials of exclusively breastfed infants with colic, at a dose of 1×10^8 cfu per day [130–133]. Sample sizes ranged from 50 to 83 in the Italian, Polish and Canadian studies. However, a larger randomised trial of the probiotic in both breastfed and for-

mula-fed infants with colic in Australia ($n = 167$) concluded it to be ineffective [134]. The most likely reasons for the Australian trial's controversial results lie in the pragmatic nature of the trial, the use of a more objective and precise measure of primary outcome, the larger sample size involved, and possibly the older age of infants recruited. It is possible that the probiotic was ineffective in infants from Australia because of undetermined differences in infant gut microbiota compared with European or Canadian infants. In addition, one of the Italian studies was not blinded [132], and both Italian studies included exclusively breastfed infants whose mothers were all on dairy-elimination diets [131, 132].

Because of this controversy, a collaboration between the authors of the five aforementioned studies is currently undertaking an individual participant data meta-analysis (IPDMA) to pool data from each individual trial into one dataset for analysis [135]. This creates sufficient power to perform subgroup analyses [136, 137]. Upcoming results from this IPDMA may inform which subgroups of infants with colic can benefit from *Lactobacillus reuteri*.

Gut Inflammation

The recent interest in the role of gut microbiota in colic has also sparked interest in examining the role of gut inflammation as a cause of colic. A recent study of 36 American term infants reported faecal calprotectin levels to be twice as high in infants with colic than those without [118]. Calprotectin, a calcium-binding protein expressed predominantly by neutrophils, is a marker of gut inflammation. It has been demonstrated to be high in faecal and serum samples of children and adults with inflammatory bowel disease [138, 139] and other paediatric inflammatory conditions such as cow's milk protein allergy [140], necrotising enterocolitis, coeliac disease and intestinal cystic fibrosis [141].

However, the link between calprotectin and colic is far from conclusive, being directly contradicted by the only other study to examine this association. This Norwegian study of 110 infants less than 10 weeks old (76 with colic, seven with transient lactose intolerance and 27 controls) and 60 children (17 with inflammatory bowel disease, 19 with recurrent abdominal pain and 24 controls) did not find a difference in faecal calprotectin levels between infants with and without colic, despite demonstrating higher levels of faecal calprotectin levels in older children with inflammatory bowel disease compared to those without [142]. This could be partially explained by the huge variability in faecal calprotectin levels found in normal healthy infants, and generally higher levels found in neonates than older children and adults [143–147]. Some authors have also suggested that faecal calprotectin levels vary by the type of infant feeding [148] and birth weight [149]. Indeed, there is a lack of consensus for 'normal cut-point' levels for faecal calprotectin in infants.

The Gut–Brain Axis

In addition to the proposed interplay of interactions between gut microbiota and gut inflammation in colic, a concept of a microbiota–gut–brain axis is emerging, suggesting a communication between gut microbiota and the brain through neural, humoral and immune pathways [150–154]. Direct evidence for an effect of gut microbiota on the brain comes from animal studies, with mice administered certain gut bacteria displaying altered behaviours [151, 155, 156]. Indirect evidence for the gut microbiota–brain association comes from clinical studies. For example, children with autism have been shown to have altered gut microbiota composition [157], and more recently an unpublished Finnish study suggested an association between early gut microbiota and later childhood behaviour [158]. The study followed up 75 infants who received a probiotic versus placebo in the first 6 months of life, and found that 13 years later the group of children who were previously assigned the placebo had higher rates of attention deficit hyperactivity disorder and/or autism diagnoses (17 % of placebo group versus 0 % of probiotic group, $p = 0.008$), with the diagnosed children having lower concentrations of *Bifidobacterium* species in their faeces in the first 6 months of life compared to the controls. This concept is particularly interesting given a link reported in two recent studies between migraine and infant colic [159, 160]. However, both studies have significant methodological limitations, such as the cross-sectional and retrospective designs, and the likelihood of recall bias. The role of the gut–brain axis in colic is a fascinating area of research that is currently far from conclusive and will require further clarification.

Summary

Despite numerous organic theories proposed to play a role in infant colic, none have been proven to be causal. The interplay between gut microbiota, gut inflammation and the gut–brain axis in infant colic is an exciting and credible concept that is currently supported by limited evidence. Meanwhile, there is still no conclusively effective dietary treatment option for infant colic. The use of hypoallergenic formulae or maternal elimination diets can be trialled for certain crying infants with other associated clinical symptoms, but do not work for all infants with colic. Anti-reflux medications are ineffective. The probiotic *Lactobacillus reuteri* may be effective in certain subgroups of breastfed infants with colic, but it is not effective where infants are formula-fed.

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Functional Diarrhea in Toddlers (Chronic Nonspecific Diarrhea)

35

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Definition and Epidemiology

Functional diarrhea in toddlers or chronic nonspecific diarrhea (CNSD) is a frequent reason for consultation to ambulatory pediatrics and pediatric gastroenterology, being the leading cause of chronic diarrhea in otherwise well children, 1–3 years of age, from a developed country [1–7]. Its exact prevalence in different geographical regions is not known, although more recently it has been reported in the developing world, where it is probably under-recognized [8]. By definition, CNSD occurs without underlying, preexistent nutrient malabsorption [6].

Clinical Presentation

The consensus committee Rome III has classified CNSD within the functional digestive disorders of infancy and childhood and defined it as follows: "… CNSD is defined by daily painless recurrent passage of three or more large unformed stools for 4 or more weeks with onset in infancy or preschool years. There is no evidence for failure-to-thrive if the diet has adequate calories. The child appears unperturbed by the loose stools, and the symptom resolves spontaneously by school age" [6]. The Rome III diagnostic criteria proper [6] are described below, in the section "Diagnosis."

The diagnosis of CNSD should come immediately to mind when facing a patient 12–36 months of age, who looks healthy, well nourished, and active and have a pattern of intermittent or nearly constant runny stools containing recognizable undigested vegetable matter [5]. As Hoekstra perceptively adds: "Every pediatrician knows the tableau vivant of extremely worried parents around a sparkling, healthy looking child who appears to be unaware of all the commotion" [5]. Not infrequently, CNSD has begun following a viral gastroenteritis. When instructed, rather vaguely, to use "plenty of clear fluids," in order to prevent dehydration, parents offer recreational clear liquids, repeatedly with the misguided belief that these constitute a physiological therapy and thus start a vicious cycle of ongoing diarrhea. Periods of improvement in stool characteristics seem to occur rather randomly while relapses may also coincide with infections (mostly upper respiratory) and other causes of biopsychosocial stress.

Pathophysiology

Given the obvious difficulty in performing prospective intervention studies on CNSD and the ethical constraints to such research, most data pertaining to this entity is retrospective (and circumstantial) and basically points to the pathogenic mechanisms discussed below.

In most cases, the mechanism of diarrhea appears, convincingly, to be related to excessive intake of fluids, particularly those with a high osmolarity, such as soft drinks and fruit juices, as well as products (and supplements) that contain fructose or sorbitol [3–5, 9]. The latter is a nonabsorbable alcohol sweetener which, when taken in certain amounts, can induce osmotic diarrhea in like manner an excess of fructose does. Several authors have reported positive (abnormal) breath hydrogen tests after intake of fruit juices rich in fructose content, by children [10–12]. It has been suggested that in patients with CNSD, the aforementioned products generate hypermotility, a notion that is in accordance with experimental studies. A pathogenic relationship exists, too, between CNSD and the ingestion of a diet low in fat [2, 4, 5, 9],

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which is plausible, as fat in the diet induces a physiological slowing of intestinal transit.

Hoekstra et al. [12] have suggested that, in apple juices, in addition to fructose, the increased presence of nonabsorbable sugars resulting from the enzymatic processing of apple pulp is an important etiological factor in CNSD. The same group has discouraged the use of fructose breath tests in children suspected of CNSD because of the considerable degree of overlapping distribution of results in the control group, which would preclude any meaningful classification of abnormal vs. normal groups [12]. Lebenthal-Bendor et al. [13] studied toddlers and infants given formulae containing modified food starch (acetylated distarch phosphate) and found that this regime increased breath hydrogen and produced loose stools and, if given together with sorbitol and fructose, it induced evident diarrhea.

The limited research that has been carried out on motility and CNSD suggests that intestinal motility is disturbed in children with CNSD [14] although the available evidence does not actually prove that this is its primary pathophysiological mechanism. Most clinicians agree that in CNSD there is a significantly shortened time in mouth-to-anus transit [5], which would be one of the explanations for the characteristic presence of noticeable undigested vegetable material in feces. In all likelihood this results from a reduced colonic transit time. In children with CNSD, food may fail to interrupt the migratory motor complex (MMC: the "intestinal housekeeper," a periodic series of physiologically excitatory myoelectric and related contractile activity) [14], perhaps owing to an "immature" gut motor development.

It is not generally well recognized that the water content of normally looking stools is 70–75 %, while in watery stools this is close to 90 %. This minor increase in water content can thus make all the difference in the parental perception of health and disease [5]. In CNSD, this increase in stool water content does not entail a true malabsorptive mechanism and can be rightfully considered a "cosmetic" disorder of the stools. When the anomalous dietary patterns are corrected and the child's diet is normalized, the typical result is a sustained return to normal stools [2–6, 9].

Diagnosis

The diagnostic criteria of CNSD, according to the Rome III consensus [6], are as follows.

- For more than 4 weeks, daily painless, recurrent passage of three or more large, unformed stools, in addition to all of these characteristics:
- Onset of symptoms begins between 6 and 36 months of age.
- Passage of stools occurs during waking hours.
- There is no failure to thrive if caloric intake is adequate.

Rome IV criteria have been recently updated and must include all of the following [15]:

1. Daily painless, recurrent passage of 4 or more large, unformed stools
2. Symptoms last more than 4 weeks
3. Onset between 6 and 60 months of age
4. No failure to thrive if caloric intake is adequate

Although CNSD was described several decades ago and has recently been validated by committees of experts [6, 9], the fact is that in general pediatric practice, this is a diagnosis that often is mislabeled. Yet, the typical clinical and dietary history of toddler diarrhea, when properly elicited, should allow the practitioner to make a prompt and informed diagnosis with minimal inconveniences and costs for the patient and family and ideally with a minimum of laboratory tests. However, the relative ease of diagnosis and simplicity of treatment of this condition are suspicious and not convincing enough to some physicians seeking a more complex pathophysiological rationale or a more "organically" based explanation. Therefore, it is not uncommon that CNSD is overlooked in the differential diagnosis of children with chronic or intermittent diarrhea, and the typical symptom cluster is often labeled as lactose intolerance or other enzymatic malfunction, food allergy, enteroparasitosis, small bowel bacterial overgrowth syndrome, or other diagnosis—popular or trendy for each geographical region, historical period, or fad cycle [16]. These provisional diagnoses are characteristically followed by the prescription of prolonged and equally unsubstantiated dietary regimes [16] that are sometimes highly costly, as well as by trials of a panoply of medications or other preparations, including antimicrobial agents, antispasmodics, or whichever product is in vogue.

While it is common in certain places that every child with chronic diarrhea is referred to a pediatric gastroenterologist, CNSD can (and should) be promptly diagnosed and treated by a proactive general practitioner or general pediatrician. The evaluation of children with chronic diarrhea requires a thorough clinical history and a sound physical examination [6]. Factors that may cause or exacerbate diarrhea, such as diet, antibiotics, products with laxative effects, and past enteric infections, should be investigated. More rarely, factitious disease is suspected, when there are inconsistencies among a patient's history, physical examination, and laboratory findings [17].

Dietary factors (already commented) are the mainstay of the history and the subsequent diagnostic rationale. When laboratory tests are performed, these should reveal no abnormalities and be consistent with a normal nutritional and absorptive status [6]. It is suggested that some alternative conditions, such as giardiasis, cryptosporidiosis, *Clostridium difficile* infection, and celiac disease (CD), be ruled out [6].

The latter does often cause a visible deterioration of the patient's nutritional status, so it is not usually a differential diagnosis that comes to the clinician's mind faced to CNSD. However, it should be kept in mind that the nutritional and anthropometric consequences of CD may not be fully evident in the short term and that in some cases, this entity does not behave "typically" in the pediatric age range and presents in a mild fashion. Powell and Jenkins have recently argued [7] that instead of using the indistinct term "toddler diarrhoea" in any young child who presents with loose stools, it is more efficient to think of potentially treatable causes. They even propose an empirical approach to treatment.

Treatment and Prognosis

In the absence of warning signs, the sound management of chronic nonspecific diarrhea should be based on the immediate prescription of a normal dietary regime, with a drastic reduction in the excessive fluid intake and the suppression of hyperosmolar and carbonated drinks and industrial juices mentioned before [5, 6]. It has also been proposed that frequent intake of cold fluids and ingestion of food between meals be avoided in order to prevent a disruption on the MMC and intestinal hypermotility. A normal proportion of fat should be restored in the diet. The use of antimicrobials, antidiarrheal medications, and elimination diets has no rational basis or therapeutic advantages and ought to be discouraged. Parents should be given advice and support in what regards the mechanisms and prognosis of CNSD [6] since they are typically confused and concerned at the persistence of symptoms and the lack of apparent improvement on the child's stool patterns. It is particularly important to avoid iatrogenic consequences, manifested mainly in the abuse of highly restrictive diets, which may cause nutritional deficiencies in the child and domestic disruption within the family.

Overall, the prognosis of CNSD is excellent. Most children will outgrow the disorder as they mature [4, 17]. Unless there has been iatrogenic nutritional deprivation, no short- or long-term effect on growth is to be expected. There is no convincing evidence that links CNSD with any later disease of the gastrointestinal tract [18].

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Functional Dyspepsia

36

John M. Rosen and Miguel Saps

The understanding of pathophysiology and clinical characteristics of functional dyspepsia (FD) have greatly evolved over the last several years. FD is a functional abdominal pain disorder (FAPD) characterized by pain or discomfort in the upper abdomen. Symptoms of dyspepsia are frequently, but not always, associated with the ingestion of a meal. Common symptoms associated with FD also include fullness, early satiety, and nausea [1]. A distinct characteristic that differentiates the bothersome symptoms of FD from irritable bowel syndrome (IBS) is the lack of association between the child's pain/discomfort with changes in bowel movement frequency or consistency. An important consideration is that the symptoms of dyspepsia may coexist with other disorders such as IBS, gastroparesis, and gastroesophageal reflux disease (GERD) which sometimes complicates its diagnosis. The recognition of this common overlap is important at the time of diagnosis in order to limit unnecessary diagnostic testing and initiate directed therapy. The diagnosis of FD is mainly clinical and based on the Rome IV criteria.

Epidemiology/Impact

Chronic abdominal pain is common in children with a subgroup of these children meeting criteria for a FAPD. Recent epidemiologic studies have shown a high prevalence of FAPDs in children of South, Central, and North America, Europe, Asia, and Africa [2–9]. Prevalence of FAPDs varies among countries, but generally falls in the range of 10–20 %. A school-based study conducted in Colombia found a prevalence of FD of 7 % [2] while another study conducted in Nigeria found that only 0.4 % of school children had FD [8]. Most children who do not meet strict criteria for a FAPD fail to meet the minimum frequency of symptoms established by the Rome III criteria (more than once monthly but less than once weekly) [10]. A US epidemiological study found that 1.4 % of children had pain or discomfort in the upper abdomen weekly, but only 0.2 % met the Rome III criteria for the diagnosis of FD [11]. FD is typically identified with lower prevalence than IBS, with overlap of the two disorders frequently occurring in adults [12] and children [13].

Chronic abdominal pain is likely under-recognized or underreported, with only 2–3 % of children having weekly pain seeking medical care [2, 14]. Despite the low ratio of consultation, FAPDs are among the most common causes of consultation to pediatric gastroenterologists. A study of new patients presenting to a single pediatric gastroenterology clinic found that functional gastrointestinal disorders (FGIDs) were the most common reason for consultation. Seven percent of children and adolescents who consulted for FGIDs were diagnosed with FD [15].

Disability related to FAPDs is substantial, with reduced quality of life for affected children. Quality of life of children with FAPDs is even lower than in children with organic gastrointestinal disease including inflammatory bowel disease (IBD) [16]. Children with FAPDs frequently miss school and have increased anxiety, depression, and worry [14, 17] as well as sleep problems [18].

The management of FAPDs has a substantial impact on health care expenses. Total annual costs associated with management of some of the most common FAPDs in children in the Netherlands are estimated to be €2512 per patient [19]. The diagnostic workup for FGIDs has been estimated to be approximately $6000 per child [20]. Cost of care of children with FGIDs has greatly increased over the last decade and is likely to continue to increase. The health care costs associated with the management of FGIDs tripled from 1997 to 2009 [21]. These enormous costs do not account for indirect costs such as work absenteeism and over the counter medications.

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Etiology

FD should be considered in the context of the biopsychosocial model that proposes that the development, persistence, and exacerbation of symptoms result from the interplay of multiple factors including early life events. The triggering event of FD is only occasionally uncovered, however it is not uncommon for a child to associate the onset of symptoms following an acute gastrointestinal infection [22]. The fact that not all children who suffer an infection develop symptoms of dyspepsia and that children with a history of gastrointestinal infection may present with different intensity of symptoms, disability, and comorbidities illustrates the importance of nonorganic factors such as the psychosocial milieu and the subject's and parents' coping skills.

The presence of a genetic predisposition may help explain the phenotypic variation in symptoms of dyspepsia. Many genetic polymorphisms have been postulated as risk factors for FD [23, 24]. However, these potential hereditary factors are not yet well understood and their role and importance is still undefined [25].

Early life events increase the risk of FAPDs including FD. Early adverse events that have been associated with an increased risk of FAPDs in children include surgical procedures [26, 27], inflammatory intestinal disease [28], cow's milk protein allergy [29], infections [22, 30], child abuse [31], and war exposure [32]. Children may be more susceptible to the effects of gastroenteritis due to their immaturity of the immune response to pathogens, intestinal barrier, and enteric nervous system. Gastrointestinal and non-gastrointestinal infections in adulthood (respiratory infection, cellulitis, urinary tract infection) [33] have also been associated with an increased risk of FAPDs. The effect of infections in children transcends the pediatric period. Children who had a *Salmonella* spp. infection have a greater likelihood of developing FAPDs as adults [34]. Parasitic infections (e.g., *Giardia lamblia*) [35] and the use of antibiotics have also been associated with the development of FAPDs [36]. However, this is not the case of every infection as pathogens such as *H. pylori* [37] and *D. fragilis* [38] do not increase the risk of developing FAPDs.

The study of the microbiome and the post-inflammatory effects of infection are emerging as an exciting and evolving field. The mechanisms that link gastrointestinal infections to the development of FD are incompletely understood. Alterations of intestinal microbes [39] may play a role in the pathogenesis of post-infectious FAPDs and post-antibiotic-use associated FAPDs. There is a complex cross-talk between the brain, gut, and microbiome. Anxiety, depression, somatization, and catastrophizing frequently precede or coexist with FAPD symptoms (including FD) and are often associated with symptom severity and treatment outcomes [40–43]. Acute stress has been shown to result in changes in microbiome, reduced number of CD4(+) T lymphocytes, and increased mast cell degranulation [44, 45]. Psychological stress affects visceral sensation and intestinal immune reaction [46, 47]. Studies have shown a bidirectional relation between the gut flora and the central nervous system (brain–gut–microbiota axis). Stress affects the intestinal microbiome composition [48] which in turn influences intestinal inflammation and permeability [49]. Stress activates the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic nervous system. This results in increased intestinal permeability and a greater influx of antigens across the intestinal epithelial barrier that activates an immune response affecting the microbiome [50]. Animal studies have also shown that alterations in gut microbiota influence social and emotional behaviors [48, 51].

FAPDs frequently overlap with other functional or organic disease and the overlap is increasingly recognized in adults and children. Children with FD are prone to have poor sleep, symptoms of orthostatic dysregulation, and headache [52]. The presence of comorbid functional disorders in a child with organic disease may confound the diagnosis or activity state of the organic disease, and affect treatment and overall disability. Children with active IBD frequently consult for gastrointestinal symptoms that may mimic a FAPD. Some of the medications used in the treatment of IBD may also lead to dyspeptic symptoms [53]. Eight to thirteen percent of children with IBD in remission also have gastrointestinal symptoms of functional origin [54, 55]. Children with IBD and FAPDs have increased rates of depression compared to children with IBD in remission who do not have FAPDs [55]. Other organic conditions have also been associated with increased rates of FAPDs in children. Some pediatric reports have associated celiac disease with FAPDs [56]. Nevertheless, the association between celiac disease and FAPDs remains controversial with one study showing no change in risk of IBS in children with celiac disease [57] while another study found a fourfold higher risk [56]. The long-term effect of celiac disease in the development of FGIDs in children is also a matter of controversy. While a study has shown that children with celiac disease on gluten-free diet are not at increased risk of developing FAPDs [58], another pediatric study found an increased risk of FGIDs with preponderance of functional constipation [59].

Weight excess has been associated with an increased prevalence of FGIDs [60] and poor treatment outcomes in children [61]. Forty-seven percent of obese/overweight children have FAPDs, nearly twice the rate of normal-weight controls [62]. Studies in adults have found that a high visceral adiposity and a high ratio of visceral to subcutaneous adiposity were associated with FD [63].

In adults the relation between BMI and the presence of FD is influenced by gender with females who are underweight

or obese having a greater likelihood of FD [64]. Obese children with FAPDs also have more severe pain and associated disability than normal weight children [61].

Pathophysiology

Intake of solid foods is associated with changes in gastric motor activity including fundic accommodation and antral grinding. Under normal circumstances these processes do not result in noxious symptoms. However, alterations in the peripheral or central nervous system or abnormal motor activity can result in the perception of pain or discomfort. Multiple pathophysiologic mechanisms have been implicated in the development of symptoms in patients with FD, including visceral hypersensitivity, electromechanical dysfunction, and eosinophilic mucosal inflammation. Understanding the mechanisms behind each patient's symptoms would be instrumental to help direct treatment. However, alterations in several mechanisms frequently occur in a single patient, complicating the testing and understanding of FD pathophysiology [65].

Abnormal visceral perception may result in abdominal pain, postprandial fullness, early satiety, or nausea. Patients with visceral hypersensitivity are prone to develop early satiety and abdominal pain with lower volumes of gastric distension. There are numerous techniques with different degrees of invasiveness used to assess upper gastrointestinal visceral hypersensitivity in the research setting, some of which are too invasive or cumbersome to be used in daily clinical care. One of these techniques includes the use of the barostat, an infinitely compliant bag that allows measuring organ pressures and compliance, and relates these values to symptom perception. The technique requires that a balloon connected to a computer be positioned in the proximal stomach allowing the recording of intraballoon volume at a fixed pressure to measure fundic tone. Evaluation of FD using gastric and rectal barostats identified predominant gastric hypersensitivity in FD, compared to predominant rectal hypersensitivity in IBS [66], although this specificity was not replicated in all studies. Barostat studies in children with FD have shown an organ-specific heightened perception to gastric distension [67] with onset of discomfort at lower distension pressures than healthy controls [68]. Although the use of a barostat is a helpful technique to understand pathophysiologic mechanisms of FD, the use of the barostat in children is cumbersome and invasive. Thus, alternative techniques have been developed such as drinking tests that are more suitable to be used in pediatric patients. A practical example of the drinking test is the water load test. Two different techniques have been frequently used for the water load test in children; children are either asked to drink water at a fixed rate until the child reports feeling full, or children are invited to drink water ad libitum for a fixed amount of time (3–5 min) with the volume being then measured. Studies with the water load test in adults reproduce dyspepsia symptoms and have shown lower maximum tolerated volumes [69, 70]. Few studies have investigated its use in children. Sood et al. established normal values for the water load test in healthy children that seemed to pave the way for use of this test to differentiate healthy children from those with FD [71]. In this protocol, children were instructed to drink as much water as possible for 3 min (rapid drinking) or until full. A later study validated the water load provocation test by correlating symptom questionnaires with the results of the test in healthy school children and children with functional abdominal pain [72]. However, a subsequent study put into question its use by suggesting that the test had poor sensitivity (62 %) and specificity (40 %) to correctly diagnose FD in children [73]. Still, the study found that children with chronic abdominal pain ingested a lower volume of water than healthy controls, a finding that is in line with the results of barostat studies. A matter of criticism of the water load test is that in the absence of feedback inhibition, as is likely to occur with the fixed time/3 min protocol, rapid gastric emptying of water could influence the results by eliminating the filling of the proximal stomach (although according to the authors this should for an error of less than 10 % of the ingested volume). Lack of filling would also make it an inaccurate test to measure gastric accommodation. In fact in adults, the results of the measurement of accommodation with the rapid drinking water test do not correlate with results obtained with the barostat [70] which is considered the gold standard to investigate proximal stomach function.

Other techniques such as the assessment of chemosensitivity to intestinal infusion have been used to assess hypersensitivity in adults with FD, but not in children. Studies using this technique have shown that duodenal and gastric acid infusion result in increased symptoms in FD patients [74, 75] while lipid infusion increases sensitivity to gastric distension and increases nausea compared to healthy controls [76].

Electromechanical Dysfunction

Visceral sensation and gastric motor function are interdependent, but this and other reviews consider them as independent factors in order to present a more clear description and understanding of the pathophysiology of dyspepsia. Normal gastric motor function serves to accommodate the large volume of a meal without resulting in discomfort (fundic accommodation) and to prepare food for digestion and initiate passage of chyme through the small intestine. Alteration of the gastric function including impaired meal induced

relaxation of the fundus [77], delayed gastric emptying, altered antroduodenal motility, and gastric electrical rhythm disturbances have been implicated in the pathogenesis of dyspeptic symptoms [65].

As previously mentioned, gastric barostat testing is a reliable but invasive and stressful instrument for the assessment of gastric accommodation. Nutrient drinking tests are a noninvasive method to estimate meal-induced gastric accommodation. The test adequately correlates with barostat studies of gastric accommodation in adults [78]. In this slow drinking isocaloric satiety test, children are given a liquid meal that will provoke meal-induced gastric accommodation. Children are instructed to drink the nutrient meal (i.e., isocaloric liquid test meal—Nutridrink, Nutricia, Bornem, Belgium) at a set rate and score their satiety on a scale. In the Hoffman et al. protocol, children were asked to grade satiety from 0 to 5 and to stop drinking when they reach a score of 5 [79]. A study using this protocol found that 93 % of children with FD had a decreased nutrient drinking capacity compared with healthy age matched controls. The impaired nutrient drinking capacity is thought to be due to poor accommodation although this has not yet been definitively proven. Children with FD had a higher satiety score than healthy controls who in turn had a higher satiety score than children who were obese. Normal values for the satiety drinking test have been published by the same group for children 5–15 years [80]. A recent study in adults comparing the drinking test with an objective measure of accommodation (Single Photon Emission Computed Tomography, SPECT) in community subjects with FD puts into question the reliability of the test. The study showed that the maximum tolerated volume of the nutrient test did not reflect gastric volume measurements in healthy controls or FD subjects [81].

Other tests have also been used in the evaluation of accommodation in pediatric patients. A study of children with chronic abdominal pain utilized ultrasound to demonstrate impairments in antral relaxation, proximal filling, and gastric liquid distribution [82]. SPECT assesses fundic accommodation using intravenous injection of radiolabelled 99mTc pertechnetate that accumulates in the gastric mucosa and allows the visualization of the stomach and changes in postprandial volume. However, this technique requires radiation and it is considered less ideal than the gastric barostat for assessing changes in gastric tone [83]. Using SPECT and MRI, 40–50 % of adults with FD demonstrated abnormal postprandial gastric volume and impaired accommodation [84, 85]. A study with SPECT showed that children with FD had decreased postprandial gastric volume change [86]. However, the correlation between accommodation and symptoms is inconsistent.

A subset of children with FD has delayed gastric emptying. Specific mechanisms of delayed gastric emptying in FD may include altered ghrelin physiology [87, 88], antral mast cell density [89], or other sources of immune activation [90]. Constipation, through the putative colo-gastric brake, was also implicated in delayed gastric emptying in FD patients [91]. Gastric emptying rate in pediatric FD has been evaluated by several modalities. Four-hour gastric scintigraphy, ^{13}C-*s platensis* and ^{13}C-octanoic breath tests, and ultrasound evaluation have demonstrated delayed emptying in a subset of pediatric FD patients [79, 86, 92, 93]. Friesen et al., using an isotope labeled solid meal, found that 47 % of children with FD had slow GE in the first hour of the meal [94]. Hoffman et al. measured gastric emptying with a breath hydrogen test and found that as a group, children with FD had slower gastric emptying [79]. However, only 26 % had an abnormally delayed gastric emptying rate. As in adult studies, there is not consistent correlation of emptying rate with reported symptom severity or satiety in children [92, 94].

Gastric myoelectrical activity was found to be altered in some children with FD. Up to 50 % of children with FD have abnormal electrogastrography (EGG) with symptoms that correlate with the abnormalities found [94, 95]. Specific abnormalities include decreased slow waves and less rhythmic activity time in both fasting and fed states [96]. Adult FD patients have similar EGG findings and also demonstrate good symptom correlation [97, 98]. Abnormal EGGs seem independent of chronic gastritis, but are associated with antral eosinophil and mast cell density in children [89, 99]. The stress response may also alter gastric myoelectrical activity [100] through HPA axis mediated pathways. A problem of the EGG technique is the low reliability of the test and the number of artifacts that are seen during the study.

In summary, the study of alterations in the electrical and motor characteristics of children with FD is important to advance the understanding of the pathophysiology of FD, but a common problem with most of the techniques is inconsistent association between symptoms and findings. A possible explanation for some of the poor correlation between symptoms and findings is the multifactorial nature of FD. Prandial state, nutrient type, mucosal inflammation, autonomic, enteric, and central neural input, distal intestinal motor function, presence of constipation, and regulatory hormones all have the potential to affect filling and emptying of the stomach as well as perception of associated symptoms. Abnormalities of any of the various motor functions of the stomach can manifest with different severity of symptoms depending on the level of visceral hypersensitivity, anxiety, or hyperawareness.

Intestinal Inflammation

Intestinal inflammation is increasingly recognized as a potential pathophysiologic mechanism in FD [101–103]. The mechanism by which these inflammatory cells relate to

dyspeptic symptoms remains unclear. A possible link between inflammation and symptoms is through motor or visceral sensory alterations. Although still preliminary, some data suggests that impaired intestinal mucosal barrier function may be related to low-level inflammation identified in patients with FD [104]. Intestinal mast cell and eosinophils are increased in some adults with IBS and FD [105, 106]. Children with FD were shown to have increased antral mast cell degranulation, and antral mast cell density was correlated with gastric dysrhythmias and delayed gastric emptying [89]. Normative data for mucosal eosinophil numbers is controversial, but location, number, and extent of degranulation are important considerations. Pediatric FD patients were found to have moderate to extensive duodenal eosinophil degranulation on electron microscopy in a small study [107]. Similar results were found in adults with FD [106]. Increased numbers of duodenal mucosal eosinophils are also demonstrated in several pediatric studies of both FD and unspecified chronic abdominal pain [108, 109].

Table 36.1 Rome IV diagnostic criteria[a] for functional dyspepsia

Must include 1 or more of the following bothersome symptoms at least 4 days per month
1. Postprandial fullness
2. Early satiation
3. Epigastric pain or burning not associated with defecation
4. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition
Within FD, the following subtypes are now adopted
1. Postprandial distress syndrome includes bothersome postprandial fullness or early satiation that prevents finishing a regular meal. Supportive features include upper abdominal bloating, postprandial nausea, or excessive belching
2. Epigastric pain syndrome, which includes all of the following: bothersome (severe enough to interfere with normal activities) pain or burning localized to the epigastrium. The pain is not generalized or localized to other abdominal or chest regions and is not relieved by defecation or passage of flatus. Supportive criteria can include (a) burning quality of the pain but without a retrosternal component and (b) the pain commonly induced or relieved by ingestion of a meal but may occur while fasting

[a]Criteria fulfilled for at least 2 months before diagnosis

Altered Peripheral and Central Nervous System

Alterations in peripheral and central nervous system function may also contribute to FD. Adult FD patients were shown to have functional and structural abnormalities in duodenal submucosal ganglia using live imaging techniques [110]. It is possible that localized inflammation is responsible for these neuronal alterations [111]. Central nervous alterations in FD and other chronic pain conditions are increasingly identified using advanced imaging techniques [112]. Examples of differences between FD adults and healthy controls include altered structure in multiple brain regions (posterior insula most significantly) by MR evaluation [113], and positron emission tomography showing upregulation of serotonin transporter (SERT) in the midbrain and thalamus [114] as well as increased cannabinoid-1 receptor availability [115].

Evaluation and Diagnosis

The symptoms of FD cannot be explained by structural, metabolic, or inflammatory disease. Pain or an uncomfortable sensation in the upper abdomen is a hallmark of functional dyspepsia, but multiple other symptoms may coexist or predominate. Nausea, early satiety, fullness, and bloating are frequently reported, and many patients will have more than one symptom. Hoffman et al., using the nutrient drink test, found that the most common dyspeptic symptoms in children with FD were early satiety (96 %), postprandial fullness (89 %), epigastric pain (79 %), and nausea (50 %) [79]. Vomiting and belching were present in only few children. Another study in a small group of children who met Rome III criteria for FD found that in addition to epigastric pain, 65 % of children manifested nausea, 63 % early satiety, and 59 % had bloating and postprandial fullness [11]. In agreement with these findings, Kovacic et al. have found that a large proportion of children with FD have nausea [1]. Pain is the only symptom among those reported in these studies that is part of the Rome III pediatric criteria diagnosis of FD. The new edition (Rome IV) of the Rome criteria addresses some of these shortcomings (Table 36.1) [116].

The pediatric FD Rome IV criteria now include two subtypes, postprandial distress (PDS) and epigastric pain syndrome (EPS). These FD subtypes previously described only in adults may be identified in pediatrics [117]. Turco et al. found that 29 % of children with FD met criteria for the adult Rome III diagnosis of postprandial distress syndrome, 24 % met the criteria or the diagnosis of epigastric pain syndrome, and 26 % met the criteria for both conditions. Only 21 % of children did not meet any of the diagnoses. PDS and EPS are shown to associate with variable outcomes and response to treatment in the adult population.

Given the variety of upper abdominal symptoms that can encompass FD and their possible overlap with other conditions, the consideration of a broad differential diagnosis appropriate to the clinical history and exam is warranted (Table 36.2). Delayed gastric emptying may exist in a subset of children with FD, and relatively common disorders such as lactose intolerance or GERD may cause upper intestinal symptoms similar to FD. Children with small bowel intestinal overgrowth may have loss of appetite and belching that may also be seen in patients with FD [118]. Multiple comorbid symptoms are sometimes recognized in association with

Table 36.2 Differential diagnosis of chronic upper abdominal pain or discomfort

Celiac disease
Eating disorder
Eosinophilic esophagitis
Functional dyspepsia
Gastritis +/− *H. pylori*
Gastroesophageal reflux disease
Gastroparesis
Giardiasis
Hepatobiliary disease
Intestinal obstruction
Irritable bowel syndrome
Lactose intolerance
Small intestinal bacterial overgrowth

Table 36.3 Red flags suggesting need for further diagnostic testing

Anemia
Arthritis (but not arthralgias)
Delayed linear growth or delayed puberty
Dysphagia
Elevated serum inflammatory markers, hypoalbuminemia, or elevated fecal calprotectin
Hematochezia
Perianal disease
Persistent vomiting
Polyuria/polydipsia
Recurrent fevers
Unexplained rashes
Unintentional weight loss
Waking at night with diarrhea

FD and other FAPDs including joint hypermobility, postural orthostatic tachycardia syndrome, and headaches [1, 119].

The severity of symptoms is highly variable and associated disability (such as school absence, and physical activity interference), anxiety, and depression are common. Patients presenting to pediatric gastroenterology practice may have increased severity compared to the population as it is known that most with chronic abdominal pain never seek medical attention [10].

Evaluation of pediatric FD and other FAPDs in the clinical setting can be limited to history and physical exam, although screening tests are frequently used. Evaluations for intestinal inflammation or obstruction are sometimes performed to rule out other potential disease with similar chronic symptoms. Screening tests including newer markers of intestinal inflammation such as fecal calprotectin have an increasingly important role in the exclusion of organic disease when FAPDs are suspected [120]. The presence of "red flags" (Table 36.3) indicates to the clinician to consider further evaluation for organic disease, although their utility has been questioned [121]. Traditional red flags include night time pain and joint pain, but a recent study found equal incidence of these symptoms in children with functional disorders and organic disease [122]. The same study identified that unexplained anemia, weight loss, and hematochezia strongly suggested inflammatory bowel disease, indicating that the presence of one or more of these red flags may indicate the need for additional diagnostic testing. The differential diagnosis for functional dyspepsia includes disorders frequently treated by pediatric gastroenterologists including GERD, eosinophilic esophagitis, celiac disease, and *Helicobacter pylori* gastritis. These disorders may present with similar symptoms to FD and if clinically suspected then evaluation may include directed diagnostic testing including pH probe, serum screening tests, or upper endoscopy with biopsy.

The diagnosis and treatment of FD can generally be completed by a primary care provider [123]. Pediatric gastroenterologists are valuable consultants when organic intestinal disease needs to be evaluated, or when initial therapy attempts are ineffective. Cost of diagnostic evaluation is up to 5-times higher in pediatric FGID patients when performed by a gastroenterologist compared to a primary care provider [124]. Upper endoscopy with biopsy (EGD) may provide vital information in specific cases. EGD can identify mucosal inflammatory disease including eosinophilic esophagitis, *H. pylori* gastritis, celiac disease, and reflux esophagitis, among other disorders. Identification of mild histologic inflammation does not preclude the diagnosis of FD or other FAPDs [101, 125]. Generally EGD in pediatric patients with functional abdominal pain has low yield and does not result in significant therapeutic change [20, 126]. Thus, EGD is not routinely recommended for all children with FD but on a case-by-case basis. Other diagnostic tests (including ultrasound, computed tomography, and X-ray) are not recommended if FD is suspected and no red flags are present [127].

Management

The primary step in management is positive identification of FD and education of the patient and family. Once the diagnosis is made, further testing can be eliminated or minimized and therapeutic options discussed. Reassurance that FD is a known diagnosis with specific therapies and favorable prognosis can alleviate the patient and parents' concerns that the symptoms are caused by a rare disease and that an extensive evaluation may be needed to uncover the cause of the child's complaints. Treatment should be framed using the biopsychosocial model, explaining the biologic and psychological components of symptom generation or maintenance. Explaining the bidirectional interaction of the brain–gut axis will help address the child's disability and the effect of stressors that may negatively impact symptoms and treatment outcomes. In addition to treatment of GI symptoms, attention

should be paid to helping the child with sleep and school problems, if those exist, and providing the patient with treatment that adapts to the patient's needs and family beliefs. Medications are often used in conjunction with complementary therapies with a goal of symptom reduction (not necessarily elimination) and return of daily function. There is little evidence to guide the treatment of FD in children. Most pediatric clinical trials were conducted on children with FAPDs in general, which in some cases included children with FD [128, 129] with only one randomized controlled trial conducted exclusively in children with FD [130]. Thus, most available data on the treatment of dyspepsia derives from expert opinion, retrospective pediatric studies [131], and literature reviews [65, 101, 132–134].

Pharmacological Therapy

In daily clinical practice, proton pump inhibitors (PPIs) and prokinetics are usually used as initial medications. Acid reduction therapy is commonly used as first-line medication mainly in cases of FD with epigastric pain while prokinetics are usually prescribed in cases of early satiety and postprandial fullness. A 3 weeks long randomized placebo controlled trial of the histamine-2 receptor antagonist (H2RA) famotidine conducted on a small group of children with FD has shown global improvement of symptoms but no beneficial effect on pain [130]. A pediatric trial compared four antisecretory agents (omeprazole, famotidine, ranitidine, cimetidine) for a period of 4 weeks in 169 children (age 2–16) diagnosed with functional dyspepsia [135]. The study showed that omeprazole was the most effective in achieving complete resolution of symptoms. Similar results were obtained in a study on adults with FD. One study showed that proton pump inhibitor (PPI) therapy was more effective than H2RA for FD [136]. A review of clinical trials in adult patients reported significant improvement in symptoms with PPI therapy [137]. These data suggests that empiric acid reduction for a limited period of time may be recommended in pediatric patients with FD.

Medications affecting visceral sensation are sometimes used to treat pediatric FD. Tricyclic antidepressants (TCAs) reduce nausea, abdominal pain, and delay gastric emptying. Amitriptyline is one of the more commonly used TCAs despite mixed results of efficacy in pediatric studies and the adverse effects related to anticholinergic and antihistaminic activity. An RCT of low-dose amitriptyline in children and adolescents with FAPDs identified high placebo effect (and high treatment effect) which made interpretation of medication efficacy difficult [138]. An earlier trial in pediatric IBS showed improved quality of life, but no clear improvement in abdominal pain [139]. A multicenter placebo controlled trial of amitriptyline in adults with FD showed modest, but significant improvement in symptoms [140]. The beneficial effect was similar to Saps et al. pediatric trial if calculated with intention to treat analysis (53 %), but the placebo effect was lower (40 %) than in the pediatric study. The study showed greater benefit in patients with pain predominant symptoms. Selective serotonin reuptake inhibitors (SSRI) were studied in a RCT of pediatric FAPDs, but did not show significant differences in symptom resolution [141]. The Talley et al. study of adult subjects with FD included an SSRI arm (escitalopram), and also did not show a benefit over placebo [140]. Prior studies of SSRIs in adults with FAPDs have shown efficacy equivalent to TCAs [142]. Given reports of cardiac dysrhythmia associated with TCA and SSRI use, it is reasonable to obtain baseline EKG to assess QT interval prior to initiation of therapy. While the use of TCAs and SSRIs is directed towards altered visceral sensitivity, their influence on gastrointestinal motility may affect symptom resolution. Two controlled studies on TCAs (nortriptyline, amitriptyline) found no benefit of these drugs in FD with delayed emptying [143]. Mirtazapine, an antidepressant with antagonism of H_1, α_2, $5HT_{2c}$, and $5HT_3$ receptors, was studied in a pilot RCT of adults with FD and weight loss [144]. Use of mirtazapine reduced dyspepsia symptom severity and improved quality of life, nutrient tolerance, and weight. An alternative strategy of targeting the specific nociceptor TRPV1 was attempted in adults with FD. A double blind, placebo controlled trial of red pepper powder in adults with FD showed initial, transient discomfort, but overall reduction on symptoms of pain and fullness [145].

Prokinetics as a class have shown mixed results in the treatment of FD in adults. A meta-analysis of prokinetics in 1844 adult FD patients found reduction in symptoms [146], but a separate study found no correlation between symptom improvement and gastric emptying rate [147]. Specific prokinetics may target 5HT, dopamine, or motilin receptors. Cisapride and other $5HT_4$ receptor agonists improve gastric emptying and accommodation, and potentially alter visceral sensitivity. However, cisapride was withdrawn from the USA and European markets due to concern for fatal cardiac arrhythmias (although not clearly a concern in healthy children [148]). In adult trials, mosapride ($5HT_4$ agonist and $5HT_3$ antagonist) demonstrated FD symptom improvement [149] although a meta-analysis could not support the effects of mosapride, possibly due to heterogeneity among study definitions and outcomes [150]. Cinitapride ($5HT_4$ receptor agonist, dopamine-2 receptor antagonist) reduced symptom severity as well as domperidone [151]. Domperidone and metoclopramide are dopamine antagonists used as prokinetic agents. Although metoclopramide is effective in FD, the potential for irreversible extrapyramidal adverse effects limits its use in pediatrics. Domperidone also improves FD symptoms in adult trials [152] and does not have similar risk of extrapyramidal adverse effects. However, due to its

potential for adverse cardiac effects, in the USA it is only available for compassionate use as an investigational drug through the FDA. Erythromycin activates antral and small intestinal motilin receptors and decreases bloating with improved gastric emptying in adult FD patients, but does not alter postprandial symptoms [153]. Other motilin receptor agonists including camicinal are promising and improve gastric emptying, but efficacy to reduce FD symptoms is not yet established [154, 155]. Another prokinetic agent, acotiamide, improves gastric accommodation through acetylcholinesterase inhibition and shows promise in treatment of adult FD in ongoing trials [156–158]. Other novel prokinetics studied in gastroparesis (e.g., relamorelin, a ghrelin receptor agonist [159]) may in the future be studied in FD patients given the overlapping spectrum of symptoms and electromechanical dysfunction of the two disorders. Botulinum toxin A endoscopically injected in the pylorus safely reduced symptoms in pediatric patients with gastroparesis refractory to conventional therapy [160], and may be considered in a similar subgroup of refractory FD patients.

Gastric accommodation is an additional target of electromechanical dysfunction in FD. Cyproheptadine antagonizes $5HT_{2a}$ and $5HT_{2b}$, histamine-1, and muscarinic receptors whose putative mechanism is improved gastric accommodation through fundic relaxation, although it may also have an effect by decreasing gastric hypersensitivity. It was found to be effective in a RCT of children with FAPDs [161], and provided symptom improvement in pediatric FD patients in an open-label trial, with few and mild adverse effects [131]. Buspirone, a $5HT_{1a}$ receptor agonist, improved accommodation in adults with FD and decreased symptom severity [162]. Other medications targeting the $5HT_{1a}$ receptor to improve accommodation include tandospirone and sumatriptan, but these have not as clearly reduced symptoms [163, 164]. Tegaserod, a 5-HT_4 agonist that was taken off of the market, was found to enhance gastric accommodation in adult patients with normal gastric emptying [165]. Ondansetron, a $5HT_3$ antagonist, improved accommodation and reduced nausea in adults with FD, but mechanical and symptom effects were not seemingly associated [166].

Neuromodulation with gastric electrical stimulation significantly improved nausea and vomiting, and improved tolerance of nutritional intake in children with dyspepsia [167]. Gastric electric stimulation was also shown to improve quality of life and global health [168] in children with excellent long-term tolerance and few adverse effects [169]. Although the technology is currently in use only in few pediatric centers, it is a promising therapy for patients with refractory symptoms.

Pediatric FD patients with duodenal eosinophilia were demonstrated to have reduction of symptoms with $histamine_{1/2}$ antagonism or cromolyn, a mast cell stabilizer [170]. Of 21 patients who did not initially respond to ranitidine and hydroxyzine combination therapy, two were lost to follow-up and 17 clinically responded (complete or nearly complete resolution of pain) with the addition of cromolyn. Treatment of a similar cohort in a placebo-controlled crossover trial showed that children receiving montelukast, a leukotriene receptor antagonist, had a greater reduction in global pain than those on placebo without having any adverse effects [171]. However, symptom improvement does not seem to correlate to mucosal eosinophil density or activation, and the mechanisms of action are not yet determined [108].

Nonpharmacologic Therapy

There are several herbal preparations that have been purported to improve chronic abdominal pain. A multicenter placebo controlled trial of STW 5 (iberogast), an herbal compound with a mechanism of action that is not yet clearly understood, showed improvement of adult FD symptoms [172, 173]. An open label trial of iberogast also showed beneficial effects in pediatric patients with FAPDs [174]. Peppermint oil seems to affect various mechanisms involved with the pathophysiology of IBS. Two studies on adult volunteers have investigated the gastric sensorimotor aspects of peppermint oil. Papathanasopoulos et al. found that peppermint oil reduces intragastric pressure and proximal phasic contractility without affecting gastric tone, accommodation, visceral sensitivity, epigastric pain, or early satiety [175] while Inamori et al. found that peppermint oil enhances gastric emptying [176]. Studies in adults and children with IBS have shown a beneficial effect of peppermint oil on IBS symptoms [177]. *Nigella sativa* (black cumin) seed oil mixed with honey, added to standard treatment with famotidine, showed reduction of FD symptoms in an 8 week randomized controlled trial in adults [178]. Similarly, *Pimpinella anisum* (anise) supplementation reduced pain in adults with FD compared to controls [179]. Rikkunshito, a Japanese herbal preparation, was studied in a multicenter randomized clinical trial of FD adults and was shown to improve pain, accelerate gastric emptying, and improve accommodation possibly through serotonergic or ghrelin mediated pathways [180]. Although ginger is used to treat nausea and enhances gastric emptying, it did not improve symptoms in an adult FD trial [181]. Various phytotherapy compounds and plant extracts such as curcumin [182] have been used with different degrees of efficacy and evidence.

Complementary Therapy

Therapies aimed at modifying psychosocial stress, catastrophizing behavior, and anxiety indirectly target visceral hypersensitivity and electromechanical dysfunction given the cross-talk between the gut, brain, and the environment.

Importantly these therapies may be more effective in conjunction with medical therapy rather than in isolation [183]. Although sometimes difficult for patients and medical providers to access due to local absence of therapists or financial constraints, complementary therapies should be considered whenever possible. Over the last few years there have been several studies of gut directed hypnotherapy [184, 185] and cognitive behavioral therapy [186, 187] showing beneficial effect in children with FAPDs. Other complementary therapies with potential beneficial effects in the treatment of children with FAPDs are biofeedback assisted relaxation therapy [183], yoga [188], and acupuncture [189].

Prognosis and Future Directions

The results of studies assessing prognosis show mixed results. A study on children with FD demonstrated significant improvement in 70 % of patients at 2 years [190], while another study showed that most patients with FAPDs improve within 12 months of presentation [191]. However, another study followed a group of children (8–16 years) evaluated for dyspepsia and 5–15 years later found more chronic dyspeptic symptoms, higher frequency of anxiety disorder, and reduced quality of life compared to controls [192]. Novel pharmacologic and nonpharmacologic therapies continue to be investigated for the treatment of dyspepsia. Ongoing efforts are needed to identify most effective treatment options and determine how best to personalize these options to individual patients. Evidence-based care strategies tailored to the needs of the individual may help optimize results by minimizing symptom severity and duration and reducing adverse medication effects. The consistent use of clinically meaningful patient-reported outcome measures across studies of FAPDs will enhance research by allowing comparisons of therapeutic trials using different interventions [193, 194].

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Chronic abdominal pain is one of the most common presenting complaints both to primary care pediatric providers and to pediatric gastroenterologists. The past three decades have witnessed a dramatic change in the way chronic abdominal pain is considered, evolving from a largely pejorative psychosocial diagnosis of nonorganic pain to one in which there is increasing evidence of abnormalities in motor, sensory, autonomic, immunologic, genetic, and psychological factors resulting in disordered brain–gut communication. During this time the Rome criteria for functional gastrointestinal disorders have been developed and updated to provide a common language describing the clinical manifestations of brain–gut disorders [1, 2]. One such disorder, irritable bowel syndrome (IBS), which commonly affects children and significantly impairs physical, emotional, social, and school functioning [3], is the subject of this chapter. In this chapter, we will provide an overview of IBS in children while describing pathophysiological mechanisms and treatments, often derived from adult data, which likely have pediatric applicability.

Epidemiology

IBS has been observed worldwide; in the United States, one study found a prevalence of 8 % in middle school and 14 % in high school-aged children [4]. Using the Rome III criteria, studies have also found similar prevalence in different countries: 19.4 % in German students [5]; 2.8–25.7 % in children from Asian countries, with a pooled prevalence of 12.41 % [6, 7]. Up to 45 % of children presenting with chronic abdominal pain in whom evaluation fails to find structural, inflammatory, or neoplastic disease have symptoms consistent with IBS [1].

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Pathophysiology

Based on the biopsychosocial model for understanding disorders of the brain-gut axis, it is likely that multiple mechanisms contribute to the development of IBS. This concept explains the widely varying clinical presentations (constipation predominant (IBS-C), diarrhea predominant (IBS-D), mixed defecation pattern (IBS-M)) as well as post-infectious versus not post-infectious symptom development. Whether these pathogenetic pathways are similar in children and adults is not known. With the exception of much greater female predominance in adults, the clinical picture is quite similar. It has been suggested that early life events such as noxious stimulation by gastric suction at birth may lead to long-term visceral hypersensitivity and cognitive hypervigilance resulting in a greater likelihood of developing functional intestinal disorders [8]. Physical and/or sexual trauma in childhood is a well-known risk factor for the development of IBS in adolescents and adults [9–11]. Obesity, shorter duration of breastfeeding, history of food allergies, and surgical events early in life have also been suggested as risk factors [10, 12–15]. Gastrointestinal infection, as discussed below, is also emerging as an important antecedent event in the development of IBS.

Altered Motility

Systematic studies of large numbers of children with IBS are currently lacking. Available studies suggest that children with IBS have lower amplitude of antral contractions and slower liquid gastric emptying compared to healthy controls [16]. Although there were no differences between the IBS subtypes, children with IBS who were exposed to recent stressful life events had a significantly lower gastric emptying rate. Data from adults have shown delayed colonic transit in IBS-C and accelerated colonic transit in IBS-D [17]. One study showed decreased rectal compliance and rectal contractile response to meals in children with IBS [18].

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Genetic Determination

The concordance rate for IBS in monozygotic twins has generally been found to be higher than in dizygotic twins. However, data suggest having a parent with IBS has a greater influence than having a twin sibling and that the hereditability of anxiety and depression may play large roles [19]. A recent study of children with functional gastrointestinal disorders (FGID; but not IBS exclusively), their parents, and their child-aged siblings showed mothers, fathers, and siblings of cases were more likely to be affected with another FGID than matching control-relatives, case-mothers having the highest likelihood [20]. It has also been proposed that gene polymorphisms involving the serotonergic, adrenergic, and opioidergic systems, as well as genes encoding proteins with neuromodulatory and immunomodulatory properties, may be important [21]. Serotonin has been particularly well studied since more than 95 % of the body's serotonin is located in intestinal enterochromaffin cells. Polymorphisms in the promoter region of the serotonin reuptake transporter (SERT) protein have been associated with different forms of IBS in adults [22]. In addition, decreased measured SERT mRNA in colonic biopsy specimens has been reported in pediatric patients with IBS compared to pediatric controls, thus supporting the role of 5-HT signaling in IBS [23]. More recently, studies have highlighted differences in the pro- and anti-inflammatory cytokine profiles in pediatric patients with irritable bowel syndrome compared to healthy controls suggesting a state of altered immune regulation: a low prevalence of the high-producer genotype for IL-10 (an anti-inflammatory cytokine) was noted in patients with IBS, resulting in lower IL-10 levels [24, 25], whereas IL-12 levels were higher in patients with IBS compared to healthy children [25]. Given its heterogeneous nature, it is likely that there are significant gene–environment interactions and epigenetic changes involved in pathogenesis of IBS [19, 26].

Visceral Hypersensitivity

Barostat studies have demonstrated rectal (but not gastric) hyperalgesia in children with IBS with lowered thresholds for pain as well as abnormal pain referral after rectal distention [27, 28]. Visceral hyperalgesia may not always correlate with symptom severity [29]. Young girls with IBS demonstrate deficient endogenous pain inhibition compared to healthy peers, independent of psychological stressors [30]. Autonomic dysfunction with increased sympathetic activity has been suggested [31].

Psychiatric Disorders and Cerebral Activation

Psychiatric disorders have been strongly associated with IBS [6, 32, 33]. Large-scale studies from several countries show increased prevalence of self-reported stress, anxiety, depression, and emotional problems in children with IBS [34–37]. Using advanced brain imaging techniques, differences have been shown in activation within the insula, prefrontal cortex, thalamus, and cingulate cortex in adults with IBS compared to healthy controls in response to visceral stimulation [38, 39]. A combination of pain and psychological distress may signify poorer long-term prognosis [40–44].

Mucosal Immune Activation and Gastrointestinal Microbiome

Evidence suggests that low-grade inflammation with increased CD3+ cells, T cells, macrophages, and mast cells may play a role in IBS [45, 46]. A study found closer proximity of mast cells to nerve cells throughout the colon in children with IBS that correlated with pain symptoms [47]. Modest elevations in fecal calprotectin levels may be seen in a minority of patients, although these alterations may be a consequence of an acute gastroenteritis or may be genetically determined [48–53]. Adult patients with IBS-D were found to have higher serum levels of microbial lipopolysaccharide (LPS) and antibodies to flagellin suggesting that immune reactivity to luminal antigens may have a role in the development of IBS-D [54]. Post-infectious IBS, especially following a bacterial infection, is well described in adults and children [48, 55]. Contrary to previous literature, a recent prospective study in children reported 28.6 % of the study participants to have developed an abdominal pain-related functional gastrointestinal disorder, including IBS, within 6 months of a viral gastroenteritis [49, 56]. Employing 16s ribosomal RNA gene sequencing techniques, studies have highlighted differences in the fecal microbiota of children with and without IBS. Specifically, a greater proportion of the class γ-Proteobacteria was identified in IBS patients vs. healthy controls. Genera such as *Haemophilus* and *Dorea* were increased in children with IBS, whereas the genus *Eubacterium* and the species *Bacteroides vulgatus* were enriched in healthy children. The altered composition appears to be associated with symptoms and stooling pattern; association with clinical phenotype was found between the genus *Alistipes* and a clinical presentation of frequent recurrent pain [57]. Rigsbee et al. detected lower levels of genus *Bifidobacterium* but higher amounts of genera *Veillonella*, *Prevotella*, and *Lactobacillus* in IBS-D fecal samples [58]. In an adult study, the microbial aberrations

characterizing IBS were more pronounced in the fecal samples than in the colonic mucosal samples [59]. Both oral antibiotics and probiotics have been shown to reduce symptoms in IBS (see below on treatment), suggesting that the altered gut microbiome may contribute to symptomatology to some degree [60, 61]. Whether these alterations are the cause of IBS or the result of the disorder itself is unclear. Dietary changes may certainly be playing a role as well [62]. Controversy exists as to whether small intestinal bacterial overgrowth (SIBO) plays a role in IBS [60]; the prevalence of SIBO was significantly higher in children with IBS in one study [63]. However, these data are largely based on lactulose breath testing rather than quantitative culture of small bowel fluid. Increased intestinal methane production has been associated with IBS-C [21, 64].

Clinical Manifestations

IBS is a chronic, recurring disorder involving a range of symptoms including abdominal pain or discomfort and disturbances in stool form and/or frequency. Symptoms may range from mild to severe and disabling, leading to significant concern for patients, families, and practitioners. Due to extensive medical testing in patients with significant gastrointestinal complaints, monetary costs, both direct and indirect, as well as quality of life costs can be high [65–67]. Several clinical guides have been proposed to aid practitioners in making a positive, timely diagnosis of IBS, while avoiding exhaustive medical testing that may be time consuming, expensive, and anxiety provoking [1, 68, 69]. Over the last decades, IBS diagnostic criteria have been refined by a succession of working teams through the Rome process, culminating most recently in the Rome IV criteria for IBS published in 2016, as a subsection of diagnostic criteria for the spectrum of functional gastrointestinal disorders [2]. To better reflect clinical experience in pediatrics and to expedite diagnosis and treatment, the Rome IV criteria for pediatrics are more inclusive than adult criteria with respect to duration of symptoms (Table 37.1) [2].

In addition to clinical criteria for the diagnosis of IBS, the Rome IV working groups have furthermore delineated 4 pediatric-IBS subtypes analogous to adults based on stool form: IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), mixed IBS (IBS-M), and un-subtyped IBS (IBS-U) [70, 71]. Studies suggest that IBS-C is the most prevalent subtype (45 %), followed by IBS-D (26 %) with up to 24 % of children with IBS changing subtype within 1 year of diagnosis [2]. Subclassification may help practitioners select more targeted therapies in clinical practice, with the caveat that symptoms may change over time and classification may not be firm. Recent data suggest that the Bristol Stool Form Scale (BSFS), which is frequently used to aid in subclassification, may not be able to accurately identify different stool types in children 6–17 years of age even if made more child friendly [72]. The modified pediatric BSFS, which reduces stool categories from 7 to 5, has been shown to have higher inter- and intra-rater reliability in children, in addition to being reliable and valid in younger children ages 6 and 7 even if the descriptors were read to them [73, 74]. Additional supporting symptoms not required to make the diagnosis of IBS but commonly observed include abnormal stool frequency, straining, urgency, gas bloat, passage of mucus, and sensation of incomplete evacuation. IBS has also been associated with other gastrointestinal, somatic, and psychological symptoms including upper gastrointestinal complaints (e.g., dyspepsia), fibromyalgia, headache, backache, genitourinary symptoms, anxiety, depression, and poor school performance [75].

Clinical Evaluation

If the practitioner highly suspects IBS based on gastrointestinal complaints that meet Rome IV criteria (Table 37.1), and the patient exhibits no alarm signs as listed in Table 37.2, specificity for IBS is high, the diagnostic yield of further testing is generally low, and no further testing is required. Functional constipation should be differentiated from IBS-C based on a

Table 37.1 Rome IV diagnostic criterion for IBS in children ages 4–18

Rome IV. Diagnostic criteria[a] *for irritable bowel syndrome*
Must include *all* of the following
1. Abdominal pain at least 4 days per month over at least 2 months associated with one or more of the following:
(a) Related to defecation
(b) A change in frequency of stool
(c) A change in form (appearance) of stool
2. In children with constipation, the pain does not resolve with resolution of the constipation (children in whom the pain resolves have functional constipation, not IBS)
3. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition

[a]Criteria fulfilled for at least 2 months prior to diagnosis

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Table 37.2 Alarm features in children and adolescents with abdominal pain and abnormal stool pattern

• Gastrointestinal bleeding
• Perirectal disease
• Fever
• Arthritis
• Persistent vomiting
• Persistent right upper or right lower quadrant pain
• Dysphagia
• Involuntary weight loss
• Nocturnal symptoms
• Family history of inflammatory bowel disease, celiac disease, and peptic ulcer disease
• Growth failure/pubertal delay

From Rasquin A, Di Lorenzo C, Forbes D, et al. Childhood functional gastrointestinal disorders: Child/adolescent. *Gastroenterology*. 2006;130(5):1527–1537, with permission

Table 37.3 Differential diagnosis of chronic abdominal pain and abnormal stool pattern

Celiac disease
Carbohydrate malabsorption
Inflammatory bowel disease
Lymphocytic/collagenous colitis
Small intestinal bacterial overgrowth
Infection
Iatrogenic (e.g., medications)

careful history and physical examination and if present, should be treated appropriately. Similarly, excessive fructose and sorbitol intake may mimic IBS-D. Unnecessary testing performed to obtain negative results increase the fear that a diagnosis is being missed and therefore should be avoided [76]. Screening for giardia should be considered in children from endemic areas [77]. It is unclear whether the prevalence of celiac disease is higher in children with IBS; a study from Italy reported a prevalence of 4 % in children with IBS compared to 1 % in the general population, whereas other studies show no increased risk [78]. There are data however, suggesting that screening for celiac disease in patients presenting with IBS symptoms may be cost effective [79, 80]. A differential diagnosis for conditions that may present similarly to IBS is provided in Table 37.3. Alarm signs may not differentiate organic disease from functional disorders, but evidence suggests that the greater the number of alarm signs present, the higher the likelihood of organic disease [81–84]. The presence of hematochezia, anemia, and weight loss in the same patient was shown to be highly predictive of Crohn's disease [81]. If any red flags are raised, initial laboratory tests to consider that are focused, relatively inexpensive, and readily available include a complete blood count, erythrocyte sedimentation rate, C-reactive protein, serum aminotransferases and albumin, urinalysis, and celiac serologies. Fecal calprotectin is being frequently utilized as a noninvasive screen for intestinal mucosal inflammation and may be superior to C-reactive protein [85]. Normal fecal calprotectin levels make inflammatory bowel disease unlikely [86]. The need for other diagnostic testing such as abdominal imaging, breath tests, and endoscopy will depend on the clinical judgment of the practitioner.

Therapy

There are many approaches to the treatment of IBS involving medications, dietary manipulations, and behavioral and physical therapies. An effective treatment plan is often multifaceted and should be individually tailored and symptom directed. It must be noted that data in the pediatric literature to support the evidence-based use of any particular treatment strategy for IBS are sparse. Most therapeutic strategies are empiric and/or are extrapolated from adult studies or from studies of recurrent abdominal pain rather than irritable bowel syndrome specifically as defined by Rome criteria.

The cornerstone of successful treatment of IBS is an effective physician–patient–family relationship based on validation of pain complaints, education, and ongoing support and reassurance for the patient and family members. Realistic goals of therapy are not necessarily to eliminate symptoms, but rather to optimize patient function, quality of life, school attendance, and extracurricular participation through a biopsychosocial approach. These goals may be achieved by alleviating symptoms using appropriately selected pharmacologic and non-pharmacologic approaches, while at the same time identifying and addressing psychological comorbidities and social factors that contribute to illness behavior. In order to set realistic expectations, goals of treatment should be made clear with the patient and family from the start. Pharmaceutical and non-pharmaceutical approaches for the treatment of IBS are shown in Table 37.4.

Drugs

Antispasmodics

Anticholinergic medications such as dicyclomine and hyoscyamine may produce symptom relief through inhibition of smooth muscle contraction. Despite their common use in clinical practice, pediatric studies are lacking and adult studies have not found clear efficacy [87, 88]. Anticholinergic side effects may include constipation, dry mouth, and urinary retention. Evidence has also been conflicting for the use of peppermint oil whose active ingredient, menthol, is thought to produce smooth muscle relaxation in the ileum and colon via calcium channel blocker properties. While less rigorous and/or smaller studies have yielded positive results for its use in the treatment of IBS [89–92], including one pediatric-specific study [93], other larger studies do not show

Table 37.4 Therapeutic approaches to irritable bowel syndrome

Medications
•Antispasmodics
•Antidepressants
•Probiotics
•Antibiotics
•Melatonin
•Chloride channel agonists
•5-HT targets (investigational in children)
•Guanylate cyclase receptor agonists (investigational in children)
•Eluxadoline (pediatric data lacking)
•Miscellaneous agents (loperamide, laxatives, antacids)
Dietary
•Limiting possible "triggers"
•Increased fiber
Behavioral approaches
•Cognitive behavioral therapy
– Psychotherapy
– Hypnotherapy
– Guided imagery
Physical therapies
•Massage
•Acupuncture
•Reflexology
•Yoga

efficacy [94]. However, despite a dearth of convincing evidence, peppermint oil is becoming more commonplace for the treatment of IBS likely secondary to its relatively favorable side effect profile and role as a "natural" remedy. Possible side effects of peppermint oil include rectal and esophageal burning.

Antidepressants

The mechanism of action of antidepressant medications for the treatment of IBS is not fully understood; it is likely complex, involving multiple targets on the brain–gut axis. Studies have suggested that benefit in IBS may be due to a combination of their psychotropic, neuromodulatory, and analgesic properties [95–98]. In the adult literature, there is strong evidence showing the benefit of tricyclic antidepressants (TCA) on IBS symptoms, particularly for IBS-D [99–101]. In pediatrics, the data are limited and somewhat conflicting. One recent trial of amitriptyline for the treatment of IBS in teenagers showed overall improvement [102], whereas another recent study in a pediatric population demonstrated that amitriptyline and placebo offer similar benefit [103]. In the adult literature, there is a limited body of evidence for the use of selective serotonin reuptake inhibitors (SSRIs) in the treatment of IBS particularly for IBS-C [95, 101, 104, 105]. However, there are no large studies for the use of SSRIs in children with IBS. In neither adult nor pediatric literature are there head-to-head trials comparing SSRIs and TCAs for use in IBS. In children with severe symptoms, especially associated with low mood, flat affect, antidepressants such as low dose amitriptyline may be necessary. Side effects for TCAs and SSRIs include fatigue, dizziness, headaches, cardiac dysrhythmias, and worsening depression. Constipation may be a side effect of TCAs, and diarrhea may be a side effect of SSRIs. Therefore, TCAs may be considered for use in IBS-D and SSRIs for IBS-C. Due to the potential side effect of cardiac dysrhythmias with TCAs and SSRIs, a baseline EKG should be considered prior to initiating therapy and dose increments. Patients on antidepressant medications must be monitored carefully for signs of depression and suicidal ideations (see Chap. 6).

Probiotics

Evidence suggests that enteric flora is a regulator of mucosal inflammation and immunity, and derangements of enteric flora may contribute to IBS symptoms. [45, 46] Probiotics, which are live microorganisms capable of inducing a beneficial effect in the host, are postulated to alleviate IBS symptoms via restoration of the normal enteric flora and downregulation of mucosal inflammation. Various strains of probiotics have been studied in adults with IBS yielding mixed results. Some trials have shown benefit for the use of certain *Bifidobacterium*, *Saccharomyces*, and *Lactobacillus* strains and VSL #3 and mixed strains of probiotics in IBS-D [61, 106–111], while others report negative results [112–116]. Pediatric-specific studies are becoming available but the results are conflicting. While some studies of children with IBS found a modest benefit for the use of Lactobacillus GG in IBS [117, 118], a different pediatric study found that Lactobacillus GG was not superior to placebo [119]. Later, a recent meta-analysis of these studies found *lactobacillus rhamnosus* GG to be effective in IBS [120]. Another crossover trial evaluating VSL#3 was found the probiotics to be safe and more effective than placebo in ameliorating symptoms and improving the quality of life in children affected by IBS [121]. Thus, even though the role of probiotics for the treatment of IBS in pediatrics remains uncertain due to heterogeneous data, there seems to be a benefit for the use of *Lactobacillus rhamnosus* GG and VSL#3 in children with the IBS-D phenotype. In addition, the lack of quality control/quality assurance with respect to the type and number of live organisms found in the myriad probiotic products sold over the counter poses an additional challenge for their therapeutic use.

Antibiotics

With some evidence suggesting that small intestinal bacterial overgrowth (SIBO) may play a role in IBS [60], the use of antibiotics for the treatment has been investigated. Several small, short-term studies have demonstrated symptomatic improvement in adult patients with IBS treated with a course of metronidazole [122] or the nonabsorbable antibiotics rifaximin [123–126]. Two large, identically designed randomized

controlled trials demonstrated efficacy of rifaximin when compared to placebo in adults with IBS-D and its benefits persisted for up to 10 weeks following cessation of treatment [127, 128]. The most common side effects reported were nausea and increase in alanine aminotransferase (ALT). Based on the results from these studies, the U.S. Food and Drug Administration (FDA) recently approved rifaximin for the treatment of IBS-D in adults. Although similar trials in the pediatric population are lacking, a prospective study of children with IBS who also had an abnormal breath test at enrollment reported improvement in abdominal pain after a 1 week course of rifaximin only in those who had a negative lactulose breath test after treatment [63]. Large, well-designed pediatric trials are necessary to establish a definitive role for antibiotics in the treatment of IBS in children.

Melatonin

Melatonin is a sleep-promoting hormone primarily secreted by the brain. It has more recently been shown to be produced in the gastrointestinal tract as well, and although the mechanism remains unclear, recent investigation suggests that melatonin secretion and metabolism may be involved in the pathogenesis of IBS [129–131]. A recent randomized controlled study found improvements in pain scores and stooling patterns to correlate with higher early morning salivary melatonin levels in males with the use of VSL#3 [132]. Other studies have shown that administration of exogenous melatonin may have a beneficial role in IBS independent of its effect on sleep [133–135]. Melatonin is a relatively safe drug that may play a role in the management of IBS due to its antinociceptive effect [136].

Chloride Channel Agonists

Lubiprostone, a bicyclic fatty acid prostaglandin E2 derivative, stimulates type 2 chloride channels in the intestine to increase fluid secretion and transit thereby improving symptoms of constipation. Lubiprostone has been US FDA approved for the treatment of adults with chronic idiopathic constipation since January 2006 and for the treatment of IBS-C in adult females since April 2008. A 2009 combined analysis of 2 phase 3, randomized, placebo-controlled studies demonstrated a higher response rate for lubiprostone compared with placebo in predominantly adult females with IBS-C [137]. An extension study of patients who had completed the abovementioned trials reported significant improvements in symptoms at 52 weeks of treatment [138]. Reported side effects of lubiprostone are diarrhea, nausea, headache, and abdominal distension. Pediatric data for lubiprostone are limited and mostly available in abstract form.

5-Hydroxytryptamine (5-HT) Targets

5-HT (serotonin) is a neurotransmitter found in the gut thought to mediate gastrointestinal sensorimotor function. Recent research investigating the role of 5-HT in the pathophysiology of IBS has shown altered 5-HT signaling in the digestive mucosa [23]. As such, alosetron, a 5-HT_3 receptor antagonist, and tegaserod, a 5-HT_4 partial agonist, have been shown to be effective in the treatment of adults with IBS-D and IBS-C, respectively [139–141]. Alosetron appears to decrease visceral sensation, prolong and reduce postprandial motility, increase colonic compliance, and enhance small bowel water and salt absorption slowing down transit time [142]. Tegaserod may increase gastrointestinal motility and alter visceral sensitivity. Alosetron, released in the year 2000, and tegaserod, released in 2002, were subsequently withdrawn from the market shortly thereafter secondary to an association with ischemic colitis and serious adverse cardiovascular events, respectively. In the United States currently, alosetron is available for the treatment of IBS-D through restricted marketing. Ramosetron, a novel 5-HT_3 antagonist was shown to provide global relief of IBS-D symptoms more frequently and effectively than with placebo in four adult randomized controlled trials [143–146]. Even though there was no reported incidence of ischemic colitis or severe constipation, long-term data on the safety profile of ramosetron is currently lacking. Prucalopride, a newer 5-HT4 agonist, is also being studied in adults, mostly for chronic constipation [147]. Pediatric data on 5-HT targets is currently lacking.

Guanylate Cyclase Receptor Agonists

Linaclotide is a peptide agonist of guanylate cyclase-C, the receptors for which are located on the luminal aspect of the enterocytes [147]. In animal studies, linaclotide has been found to stimulate intestinal fluid secretion and transit and decrease visceral hypersensitivity [148]. Several large phase IIB and III trials have shown potential benefit for constipation and IBS-C and linaclotide recently was approved by the US FDA for these indications [149–151]. A head-to-head comparison using placebo-controlled model inputs found linaclotide to have higher treatment response rates and lower per-patient costs compared to lubiprostone [152]. Safety and efficacy of linaclotide have not been established in patients younger than 18 years and a black box warning exists for its use in children 6 and younger.

Miscellaneous

Eluxadoline, a mixed μ-opioid receptor agonist, δ-opioid receptor antagonist, and a k-opioid agonist, was recently US FDA approved for the management of IBS-D in adults. The safety and efficacy of Eluxadoline was established in two double-blind, placebo-controlled clinical trials in which the drug was more effective in reducing abdominal pain and improving stool consistency than placebo over 26 weeks of treatment [153, 154]. The most common side effects in patients in the treatment arm were constipation, nausea, and abdominal pain, whereas serious side effects included sphincter of Oddi spasm and pancreatitis. Pediatric data are currently lacking.

Other symptom-targeted agents that are often used in patients with IBS include loperamide for the treatment of associated diarrhea and various laxatives (e.g., polyethylene glycol 3350) for the treatment of constipation. Antacids, promotility agents (e.g., metoclopramide, erythromycin), and antiemetics are used to target nausea and dyspepsia.

Dietary Approaches

Fiber

Dietary supplementation with fiber is often used as a first-line approach in patients with IBS-C, particularly in the primary care setting, but its use is controversial [155]. Fiber is postulated to shorten intestinal transit time, thereby alleviating constipation and decreasing intracolonic pressure. Adult studies have shown that fiber may improve both constipation and diarrhea associated with IBS but not pain alone, and this was reflected in a recent randomized, double-blinded pediatric pilot study on guar gum [156–159]. Psyllium may reduce pain frequency in children with IBS. On the contrary, evidence suggests that insoluble fiber, in particular, may actually worsen pain in IBS due to increased gas bloat [158]. Therefore, limited data on the use of fiber in recurrent abdominal pain in children do not suggest clear benefit [160, 161].

Elimination Diet

Many patients perceive their IBS to be triggered by food [162, 163] and often want to discuss the role of food in their condition. As mentioned earlier, composition of the diet can induce symptoms in IBS. A diet eliminating fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) has been shown to be of benefit in adults, especially in the IBS-D subtype [164]. Various meta-analyses, systemic reviews, and randomized control trials in adults support the use of a low FODMAP diet [165–167]. Furthermore, dietitian-led FODMAP group education was found to be clinically and cost effective [168]. In a pilot double-blind crossover trial, children with IBS who were placed on a low FODMAP diet had improvements in both pain frequency and severity in addition to lesser pain-related interference with activities. Stool microbiota and metabolites differed between responders and nonresponders, suggesting the role of diet in the pathogenesis of IBS [169]. Although the FODMAP-restricted diet may be effective in short-term management of selected patients with IBS, pediatric data on long-term consequences are lacking. Other commonly identified dietary offenders are milk, wheat, eggs, and coffee. Given the difficulty for patients in maintaining elimination diets and the risk of imbalanced nutrition particularly in the pediatric population, further studies are needed to validate dietary elimination as a treatment for IBS.

Oral serum-derived bovine immunoglobulin/protein isolate (SBI) was recently evaluated as nutritional therapy for adults with IBS-D in a randomized, double-blind, placebo-controlled trial [170]. A dose of 5–10 g/day was well tolerated and resulted in improvements in both symptom days and daily symptom scores. Additional studies with larger numbers of subjects are needed to validate these findings. Pediatric studies evaluating SBI in IBS-D are ongoing.

There have been several recent studies linking IBS with higher food-specific IgG levels [171, 172] and positive skin prick testing [173], suggesting a potential role for directed food elimination in the treatment of IBS. However, this association is currently weak, and further investigation is therefore needed.

Psychological Therapies

Techniques used by therapists may include psychotherapy, guided imagery, progressive muscle relaxation, and gut-directed hypnotherapy, with the aim of developing symptom coping skills. Two pediatric-focused systemic reviews of psychological interventions (including cognitive behavioral therapy) concluded that such therapies were slightly superior to usual care [174, 175]. Since then, several pediatric studies have shown the effectiveness of cognitive behavioral therapy for treatment of functional gastrointestinal disorders, including IBS, with evidence of long-term efficacy, although one trial showed no benefit [176–180]. Gut-directed hypnotherapy was found to be beneficial in two randomized control trials [181, 182]. Treating coexisting anxiety and depression may be of additional benefit [183] (see Chap. 6).

Physical Therapies

Although massage therapy, acupuncture, yoga exercises, and reflexology have been proposed as potential treatments for IBS, there is only limited evidence to support their use.

Summary

Irritable bowel syndrome (IBS) is a commonly encountered pediatric functional gastrointestinal disorder with varying clinical presentations. Multiple mechanisms likely contribute to its development and may include visceral hypersensitivity, altered gastrointestinal microbiota, mucosal immune activation, psychiatric disorders and cerebral activation, and altered gastrointestinal motility. The recently refined pediatric Rome (IV) criteria are more inclusive than adult criteria with respect to duration of symptoms and aid in diagnosis while avoiding exhaustive, low-yield medical testing. Although a myriad of therapeutic options are available for the treatment of IBS including medications, dietary manipulations, and behavioral

and physical therapies, convincing evidence-based pediatric data to support any particular treatment modality is sparse. An effective management strategy is often multifaceted and should be individually tailored and symptom directed. Previous studies have demonstrated a particularly high placebo rate for the treatment of IBS [184], suggesting that with a strong physician–patient–family relationship, patients will improve regardless of the treatment approach. Future research in IBS will continue to focus on the pathophysiology of this disorder and on the discovery of more targeted therapies. Lastly, pediatric trials investigating the safety and effectiveness of therapies approved in adult IBS are warranted.

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Functional Abdominal Pain

38

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Functional gastrointestinal disorders (FGIDs) encompass a cluster of symptoms resulting from disorders of gastrointestinal (GI) function or central processing of information originating from the GI tract. Abdominal pain is one of the most common symptoms associated with FGIDs in children such as functional dyspepsia, irritable bowel syndrome, abdominal migraine, and functional abdominal pain (FAP). Although Rome criteria have differentiated pain-associated FGIDs into distinct categories, a degree of overlap exists. It is therefore not unusual for patients to fulfill symptom-based criteria for two or more FGIDs. Further confusion can occur when we label these disorders "functional," as some people may not understand what "functional" means. In the past, poorly descriptive terms such as idiopathic, chronic, and recurrent abdominal pain have been used to describe children with FAP. Since "recurrent abdominal pain" can be caused by many disparate conditions and does not necessarily reflect the functional nature of abdominal pain, experts in the field have recommended that this term should not be used to describe children with FAP. In this chapter, FAP implies children who fulfill the Rome criteria for FAP and, as per definition, have no identifiable cause for the pain. The term includes subjects and studies that have referred to this disorder as recurrent abdominal pain in the past.

Definition

The Rome diagnostic criteria are widely used in research studies and are now being adapted for use in clinical practice. According to the Rome III criteria, childhood FAP is classified as abdominal pain which occurs at least once per week for at least 2 months, it can be episodic or continuous, and there are insufficient criteria for other FGIDs. There should be no evidence of an inflammatory, anatomic, metabolic, or neoplastic process that can explain the subject's symptoms [1]. Children with abdominal pain at least 25 % of the time with loss of daily functioning or somatic symptoms such as headaches, limb pain, and/or difficulty sleeping should be classified under childhood functional abdominal pain syndrome [1]. This definition is a description of symptoms, critics think it is too general, and there are very few studies which have attempted to validate the accuracy of the Rome criteria in clinical settings.

Since the Rome criteria require the clinician to exclude inflammatory, anatomical, and metabolic disease process before diagnosing FAP, some diagnostic testing is inevitable. Alarm symptoms that are more likely to occur in the presence of an organic disease have been proposed to circumvent this issue, but there is little clinical data regarding their accuracy (Table 38.1). Proponents of the biopsychosocial model recommend that in the absence of alarm symptoms, a presumptive diagnosis based on symptoms can be made and help avoid a diagnostic workup which is invariably negative in FAP. Recent studies suggest that the introduction of the Rome criteria has not altered physician practice behavior and diagnostic testing is still common in children with FAP [2, 3]. There are no evidence-based guidelines regarding which organic disease must be excluded or which tests are helpful before diagnosing FAP. For instance, recent data show low yield of celiac screening for patients meeting symptom criteria for FGIDs [4, 5]. Less than half of children diagnosed with functional abdominal pain by general practitioners fulfill published criteria [6]. A recent survey study suggested that the vast majority of gastroenterologists do not feel that the Rome criteria are very useful in clinical practice, and further work to validate the Rome criteria is needed [7]. The Rome III criteria are currently undergoing refinement.

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Table 38.1 Alarm symptoms suggestive of an organic disease in children with chronic abdominal pain

Symptoms
Involuntary weight loss
Vomiting especially bile or blood
GI blood loss
Unexplained fever
Persistent right upper or lower quadrant pain
Delayed puberty
Family history of IBD
Dysuria, hematuria, or flank pain
Examination
Scleral icterus, pale conjunctivae
Rebound, guarding, or organomegaly
Perianal disease (skin tags, fissure, fistulae)
Occult or gross blood in the stool

Epidemiology

In Apley's original survey of 1000 primary and secondary school children, 10.8 % of the children were found to have recurrent abdominal pain [8]. Subsequent studies have reported a prevalence of 0.3–25 % in school-aged children [9]. The wide variability in estimated prevalence is likely to be due to different definitions and diagnostic criteria used to define FAP in these studies. Functional abdominal pain accounts for approximately 2–4 % of pediatric clinic visits and almost 25 % of the referrals to tertiary gastroenterology clinics [10]. Most studies evaluating symptoms in groups of children suggest there are two peaks in prevalence of FAP: one between 4 and 6 years of age and the second between 7 and 12 years of age [11, 12]. In contrast, Perquin et al. demonstrated a progressive rise in symptoms of RAP in children below 12–15 years of age [13].

The original study by Apley reported a slight female predominance with a female-to-male ratio of 1.3:1 [8]. Subsequent studies which included children and adolescents reported a female-to-male prevalence ratio of 1.4:1 [9]. Gender differences in the prevalence of FAP are not obvious in children younger than 8 years of age. In boys the prevalence in 5–10-year-olds is 10–12 %, after which there is a slight decline followed by a later peak around 14 years of age. In girls there appears to be a sharp increase in reported incidence of abdominal pain after the age of 8 years [9, 13]. One study of adolescents in a suburban town in the USA reported no significant difference in prevalence rates among males and females, although strict criteria for FAP were not applied [14].

Pathophysiology

Functional abdominal pain is thought to be a multifactorial disorder resulting from a complex interaction between psychosocial factors, familial genetic vulnerability, environmental factors, and earlier life experiences through the brain–gut axis (Fig. 38.1). The bidirectional brain–gut interaction in functional GI illness is well recognized. The brain receives a constant stream of input from the GI tract and integrates this with other interoceptive information from the body and the environment. It then sends an integrated response back to various target cells within the GI tract [15]. In healthy subjects, the majority of the interoceptive information reaching the brain is not consciously perceived but serves primarily as input to autonomic reflex pathways (Fig. 38.1). In children with FAP, the conscious perception of the interoceptive information or recall of interoceptive memories of such an input can result in constant or recurrent pain. The model which incorporates peripheral and central abnormalities in patients with FAP is plausible, but *until recently was* somewhat assumptive as the majority of the data this model is based upon are extrapolated from animal and adult human studies.

Visceral Hypersensitivity

An afferent signal originating in the GI tract activates the nerve endings in the bowel wall and travels along the first-order spinal afferents, which synapse with the second-order neurons in the dorsal horn of the spinal cord. The second-order neurons project to the brain through the spinoreticular, spinomesencephalic, spinohypothalamic, and spinothalamic tracts. While the first three tracts mainly activate unconscious and autonomic responses to visceral sensory input including changes in emotion and behavior, the latter transmits conscious sensation by its projections to the somatosensory cortex, anterior cingulate cortex, and the insula. The spinothalamic pathway is mainly responsible for pain localization and assessment of pain intensity, and the other three pathways modulate affective pain behavior with stimulation of important autonomic and descending inhibitory pathways (Fig. 38.1). In animal models, the anterior cingulate cortex and its projections to the amygdala and periaqueductal gray matter of the midbrain and the rostral ventromedial medulla and the dorsolateral pontine tegmentum can selectively modulate nociceptive transmission. Stimulation of these sites inhibits responses of spinal neurons to noxious stimuli and can have an analgesic effect [16]. Therefore, second-order spinal neurons are activated by afferent input from the first-order neurons conveying messages from the bowel and inhibitory input from the brain. Traditional thinking assumes that disruption in this balance can result in hypersensitivity.

Peripheral sensitization represents a form of stimulus-evoked nociceptor plasticity in which more prolonged stimulation, especially in the context of inflammation or injury, leads to change in the chemical milieu that permits nociceptor firing at a lower level. The main sensitizers implicated in primary sensitization include bradykinin, histamine, serotonin,

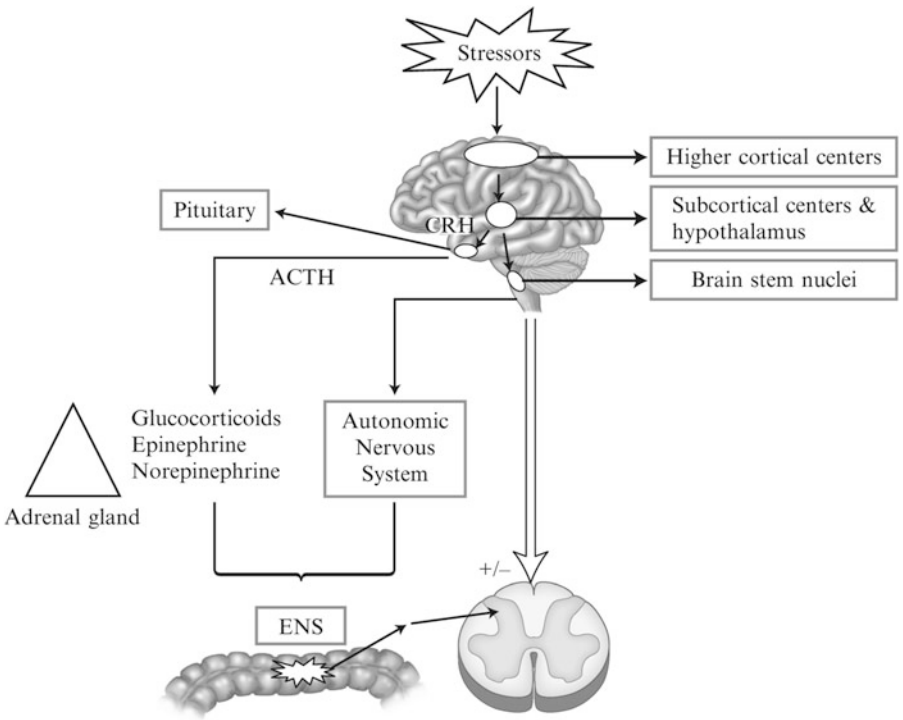

Fig. 38.1 Schematic representation of interaction between the sensory neuronal pathways and stress-related activation of the hypothalamic–pituitary–adrenal axis. The GI afferent stimulus perception is modulated by these interactions. Following activation of cortical and subcortical brain regions, increased quantities of corticotropin-releasing hormone (CRH) induces the release of adrenocorticotropin (ACTH) from the anterior pituitary. This in turn stimulates the release of glucocorticoids from the adrenal glands. In response to ANS activation, cells of the adrenal medulla produce catecholamines such as adrenaline and noradrenaline. These have potential to modulate activity of the sensory neuronal pathways and cause visceral hypersensitivity. The cortical and subcortical brain centers can facilitate or inhibit the activation of second-order spinal neurons in response to visceral afferent stimulus. (Adapted from Knowles CH, Aziz Q. Basic and clinical aspects of gastrointestinal pain. Pain. 2009;141:191–209, with permission.)

proteases, and cytokines [17]. Persistent abdominal pain following a gastrointestinal infection, surgery during infancy [18], or an inflammatory disorder such as gastroenteritis, Henoch–Schonlein purpura, and cow's milk intolerance can alter pain perception, and visceral hypersensitivity is thought to be one of the mechanisms responsible for this change [19–21].

Central Sensitization

Under physiological states, spinal afferents respond only to noxious stimuli, but under conditions of injury and inflammation of peripheral nerve endings or repetitive noxious stimulation, they can respond to lower intensity afferent signal, a phenomenon called central sensitization [15]. Central sensitization can also affect adjacent neurons, leading to the recruitment of previously "silent" nociceptors and hyperalgesia in regions (somatic and visceral) remote to the site of peripheral sensitization. This is also termed secondary hyperalgesia. In animal models, this facilitation is triggered by presynaptic release of neurotransmitters and increased intracellular calcium, which lead to phosphorylation of *N*-methyl-D-aspartate (NMDA) receptors and resultant changes in receptor kinetics. Substance P and other tachykinins play a crucial role in central sensitization [17, 22]. Descending projections from the brain stem nuclei to the spinal cord enhance or reduce the excitability of dorsal horn neurons, which receive afferent input from the viscera, in part through the opioidergic and adrenergic descending pain inhibitory pathways. Using the water-drinking test and barostat studies, altered sensory gastric perception and visceral hypersensitivity have been reported in children with FAP [23–25].

This traditional view that chronic pain disorders are either driven by primary afferent input (e.g., post-infectious irritable bowel syndrome) or sustained by the local reverberating circuitry within the spinal cord and facilitated by descending pain modulation has been challenged. In the last decade advances in functional brain imaging has helped in identifying key neural structures involved in processing experimental gut stimulation [26, 27] The human brain is intrinsically organized into distinct functional networks supporting various sensory, motor, and cognitive functions [28]. Of particular relevance to the understanding of visceral hypersensitivity and altered brain–gut interaction in IBS is an intrinsic brain network, the salience network (SN), with two key anchor nodes in the anterior insula (AI) and anterior cingulate cortex (ACC) [29]. The SN has extensive connections with cortical and subcortical brain structures, such as the medial prefrontal cortex, thalamus, amygdala, cerebellum, and midbrain structures. Pain produced in the absence of tissue injury (e.g., FGIDs) and pain relief in the absence of drugs (e.g., placebo analgesia) provide compelling evidence that salience—how we interpret the importance of a given physiological state—is able to reproduce experiences to those produced by overt tissue injury or potent analgesic medications. A number of studies using controlled rectal distension as the

stimulus have shown greater engagement of regions of the salience network in IBS patients [27]. Our group evaluated changes in the brain networks in a small cohort of pediatric patients with chronic visceral pain and emphasized the crucial role of the SN in modulating the engagement of the executive control network and disengagement of the default mode network (brain activity during mental rest) when attending to a salience event (e.g., rectal distension) [30].

It has also become clear that some of the brain circuitry involved in processing pain-related information can be engaged by social and emotional experiences such as viewing another individual in pain, and these experiences appear to selectively involve neuro-circuitry related to emotional rather than sensory aspects of pain. Viewed in the context of a more comprehensive conceptual framework, rather than the narrow viewpoint of nociceptive processing, IBS symptoms can be defined by dysfunctions in a generalized model of visceral homeostatic regulation network within the brain–gut axis, regulating not only physiological conditions of viscera, but also the associated emotional and motivational contents [31]. Children with FAP appear to be temperamentally anxious and suffer from emotional difficulties. Such temperamental traits have been associated with pessimistic worry, fear of uncertainty, harm avoidance, and a lowered response threshold to environmental challenges [32–36]. Children with a high pain dysfunctional profile have been characterized by poor coping skills, negative affect, pain catastrophizing, higher disability, and enhanced pain sensitization several years later [37].

Early Life Events and Environment

Early life stress can also influence illness behavior and emotional response to pain [38]. Work in animal models suggests that severe, prolonged, or repetitive pain can trigger neurobiological changes that can permanently modify pain pathways [39]. These changes are likely to be mediated through the hypothalamic–pituitary–adrenal axis [40–42]. A higher incidence of FGIDs and psychiatric comorbidities has been reported in adults who were abused as children [43–45]. A recent meta-analysis reported a 2.7 higher risk of functional somatic syndromes in individuals exposed to trauma as young [46]. What constitutes a painful or a potential sensitizing event is not clear. Painful experiences in neonatal life have been related to altered pain processing and hypersensitivity in later life [47, 48]. A stressful life event such as marital turmoil in the family, school bullying, and being involved in an accident can predate the onset of FAP. Therefore, stressful life events both early and later on in life seem to be a common in children with FAP. Corticotropin-releasing factor is an important hormone involved in stress response and can alter GI motility and visceral sensitivity [49].

Parenting style can influence a child's ability to cope with pain. Children of parents who have IBS report more bothersome gastrointestinal symptoms compared to control children [50]. They also have more school absences and physician visits for gastrointestinal symptoms [51]. Twin studies have shown that the presence of IBS in the respondent's parents made a larger contribution to the risk of having IBS than did the presence of IBS in one's twin, suggesting social learning is more important than the environmental factors in determining illness behavior [52]. Further support for social learning in determining illness behavior comes from research showing a relationship between parental responses and children's behavior [9]. Higher levels of parental solicitousness in response to their child illness behaviors are related to higher levels of children's symptoms and disability as measured by school absences. Factors associated with solicitous behavior include non-Caucasian race, lower educational status, single mother or no partner, and parental perception of severity of their child's condition [9, 11].

Clinical Presentation and Evaluation

Functional abdominal pain is typically periumbilical and usually not associated with vomiting, weight loss, diarrhea, nocturnal symptoms, or growth deceleration. Organic abnormalities have been reported in 25–88 % of children with recurrent abdominal pain [53–55]. However, the causal relationship of some of the reported abnormalities with abdominal pain is not clear. A good example is the relationship of *H. pylori* infection with abdominal pain; four studies assessed this and none found a positive association [50, 56–58]. A systematic review of the utility of endoscopy in FAP found a 28 % diagnostic yield when *H. pylori* was considered a diagnostic (vs. 3.6 % as incidental) finding [59]. Therefore, studies reporting positive yield of upper endoscopy in children with abdominal pain may overestimate the positive yield of upper endoscopy if they include *H. pylori* infection as an association with abdominal pain.

The majority of the GI disease that presents with abdominal pain as a symptom can be differentiated from FAP by a careful history and clinical examination (Table 38.2). Prandial or postprandial pain may be associated with pancreatobiliary disease, peptic ulcer, allergic disease, and carbohydrate intolerance. Postprandial release of cholecystokinin stimulates gallbladder contractions and pancreatic secretions. These physiological events can induce pain in subjects with biliary tract obstruction and pancreatitis. Children with constipation and rectal fecal impaction can also present with postprandial pain [55]. The gastrocolonic reflex after the meal can result in cramping pain in the presence of hard stool in the rectum producing outlet obstruction. Intolerance to lactose or sucrose or from excess fructose or sorbitol ingestion in fruit juice can

Table 38.2 Differential diagnosis of functional abdominal pain

GI tract
Gastroesophageal reflux disease
Peptic ulcer disease
Esophagitis (peptic, eosinophilic, or infectious)
Celiac disease
Carbohydrate intolerance
Parasitic infestation
Inflammatory bowel disease
Malrotation and volvulus
Intussusception
Meckel diverticulum
Chronic appendicitis
Epiploic appendagitis
Gastric emptying abnormalities
Small intestinal bacterial overgrowth
Gall bladder, liver, and pancreas
Cholelithiasis
Choledochal cyst
Hepatitis
Liver abscess
Recurrent pancreatitis
Genitourinary
Urinary tract infection
Hydronephrosis
Urolithiasis
Dysmenorrhea
Pelvic inflammatory disease
Endometriosis
Other
Gilbert's disease
Familial Mediterranean fever
Malignancies
Porphyria
Hereditary angioedema
Sickle-cell crisis
Lead poisoning
Vasculitis (e.g., Henoch–Schonlein purpura)
Thyroid disorders
Anterior cutaneous nerve entrapment syndrome
Psychiatric disease

also cause pain, bloating, and diarrhea [60–62]. A detailed dietary history can help to identify dietary triggers and food intolerance, which can present with abdominal pain. The "ritual" of this process provides important information and further assures the patient that the physician takes their complaints seriously and is seeking a cause.

Identification of troublesome symptoms, possible triggers, environmental stressors, social or emotional disturbances, impaired daily functioning, and underlying psychiatric conditions is helpful in excluding other diagnosis and comorbid conditions. It also helps to develop a patient-specific management plan. Older children and adolescents should be interviewed without their parents and assured of complete confidentiality. Physical and sexually abused children often present with functional GI symptoms [63, 64].

Children with periumbilical abdominal pain and no alarm features usually do not require investigations. If the symptoms do not improve with empiric therapy or there is a high suspicion of an organic disease process, investigations including a complete blood count, erythrocyte sedimentation rate, C-reactive protein, urine analysis, and culture are justified [1, 3, 65]. Other investigations such as biochemical profiles (liver and kidney), stool culture and examination for ova and parasites, and breath hydrogen testing for sugar malabsorption can be performed at the discretion of the clinician. The decision to perform these investigations is based on the child's predominant symptoms, degree of functional impairment, and parental anxiety. Plain abdominal X-ray is not a reliable investigation to diagnose constipation, except when a rectal fecal mass is suspected. Repeated negative laboratory and imaging studies can provoke anxiety, and the child may start thinking that the physician is unable to find a cause for the symptoms and a rare and unusual disease process is being missed.

In one prospective study, three trajectories based on symptom severity, psychological evaluation, functioning, and self-worth evaluation were identified [66]. Almost 70 % of the subjects with low levels of symptoms and functional impairment improved within 2 months and had no recurrence at 1- and 5-year follow-up. All had low levels of anxiety and depression and scored better on self-worth compared to children in the other groups. The second trajectory classified as the short-term risk group had highest level of symptoms and functional impairment, but less severe depressive and anxiety symptoms. Symptoms in most of these patients improved in a few months, and they had no relapse in symptoms at 5-year follow-up. The third trajectory, classified as the long-term risk group, included children (14 %) with high levels of symptoms and functional impairment. All had high levels of anxiety and depressive symptoms, more negative life events, and lower perceived self-worth. Children in this group had persistent symptoms during the 5-year study period. It appears that children in the short-term and long-term group would benefit from referral to a specialist center, which has access to a multidisciplinary team including a gastroenterologist with an interest in pain-associated FGIDs and a pain psychologist.

Management

When evaluating children with FAP, it is important to allocate sufficient time for the consult in order to allow the child and family to share their concerns. This assures them that the physician is listening and their complaints are being taken seriously. It is important to explain the pathophysiology of

visceral hypersensitivity in a simple and child-friendly language. Establishing reasonable goals for improvement enables the physician to provide positive feedback and helps to maintain trust in the physician–patient relationship. Patients with prolonged or severe symptoms and a complex behavioral overlay that interfere with participation in a treatment plan may require early referral to a specialist center.

Psychological Therapy

Cognitive behavioral therapy (CBT) is based on the belief that our thoughts, behaviors, and feelings interact and aims to reduce or eliminate physical symptoms through cognitive and behavioral changes. Cognitive behavioral therapy guides patients to modify or change cognitive distortions or irrational, negative thinking to improve mood and functioning. Parental response to pain reports and beliefs about the significance of pain and levels of psychological distress in the child can affect the severity of GI symptoms and disability. Cognitive behavioral therapy would guide a patient who believes that his or her pain is a symptom of undiagnosed terminal illness to challenge this belief and consider substituting a more realistic thought, such as that the pain is likely to subside and does not represent a terminal illness. Several randomized controlled trials to test the effectiveness of pain interventions in children, using a self-management approach that includes components of CBT and involvement of parents in treatment, yielded encouraging results (Table 38.3) [67–71]. However, methodological limitations in some of these studies have made interpretation of results difficult. A recent Cochrane review thought CBT is worth considering for some children with functional abdominal pain, but better quality studies to show the efficacy of CBT are needed [72]. The American Academy of Pediatrics also rates CBT as efficacious in the treatment of FAP [73]. Recent guidelines for addressing anxiety in children with FAP have been suggested by Cunningham et al. [74].

Relaxation treatments guide patients to reduce psychological distress by achieving a physiological state that is the opposite of how the body reacts under stress. Common relaxation techniques include abdominal breathing, progressive muscle relaxation, guided imagery, hypnotherapy, and biofeedback. Guided imagery directs patients to imagine themselves in a peaceful scene to create an experience that is incompatible with stress and anxiety. The peaceful scene is individualized for each patient and is visualized with sufficient sensory detail to absorb the patient's attention. Biofeedback is an approach that uses instruments to detect and amplify specific physical states in the body and help bring them under one's voluntary control. The mechanism of pain relief is based on specific physiological changes caused by the biofeedback. Selected physiological functions are measured such as heart rate, skin temperature, galvanic skin response, or electromyogram. Hypnotherapy includes three sequential elements: hypnotic induction, deep relaxation, and suggestion. Hypnotic induction is produced usually by eye fixation, and this sets the stage for the relaxation and deepening phases, which may incorporate the deep breathing, visualization, and muscle relaxation strategies. Once a state of deep relaxation is achieved, hypnotic suggestions are made, such as the pain is leaving your body. A recent systematic review on hypnotherapy in children with FAP showed significantly decreased abdominal pain severity in all trials included [75]. Most of the studies evaluating the role of relaxation therapy in FAP have reported beneficial effects [76–80]. Cognitive behavioral and relaxation therapies are emerging as the first-line treatment for children with FAP; larger and better designed studies in the future will help to confirm their beneficial effect in FAP.

Diet

Food triggers such as caffeine, fatty or large meals, carbonated soft drinks, and lactose, which exacerbate pain or gastrointestinal symptoms, should be identified, with an attempt to modify them. Lactose and fructose elimination may be useful in a small subset of patients [61, 62]. Dietary fibers may be helpful in some patients [81, 82] although two recent randomized trials show opposing results [83, 84]. Supplementing fiber can cause bloating, which may be distressing for some patients. A Cochrane review reported that there is a lack of high-quality evidence on the effectiveness of dietary interventions in children with recurrent abdominal pain. The authors also recommended that there was no evidence that fiber supplements, lactose-free diets, or Lactobacillus supplementation are effective in the management of children with RAP [85].

Pharmacotherapy

Antisecretory drugs are commonly used to treat children with abdominal pain, but their efficacy has not been evaluated. A double-blind placebo crossover trial evaluated the improvement in pain and global assessment scores in 25 children with abdominal pain. There was improvement in global assessment scores, but not in abdominal pain scores in children treated with famotidine compared to placebo [86].

Tricyclic antidepressants act primarily through noradrenergic and serotonergic pathways. They also have antimuscarinic and antihistaminic properties and are used as first-line migraine prophylaxis. Tricyclic antidepressants with sedative properties can help children with sleep disruption and FAP as well as comorbid migraines. But their role in treatment of

Table 38.3 Studies using psychological therapy (CBT) to treat FAP in children since 1990s

Article	Population and study design	Intervention/control	Outcome
van der Veek et al. (2013)	*n* = 104, 7–18 years	CBT	CBT equally effective as IMC in reducing pain (60 vs. 567 %), GI symptoms, functional disability and quality of life
	RCS	•Relaxation training	
		•Cognitive restructuring	
		•Coping strategies for child and parents	
		•6 sessions	
		Control group (IMC):	
		•6 physician visits	
		FU: 12 months	
Levy et al. (2010/2013)	*n* = 200, 7–17 years	CBT	Greater decrease in pain and GI symptoms in CBT group
	RCS	•Relaxation training	Less parental solicitous responses in CBT group
		•Modify family response to illness	Outcomes maintained long-term
		•Cognitive restructuring	
		Control group:	
		•Educational support	
		•3 sessions each group	
		FU: 12-month posttreatment	
Duarte et al. (2006)	*n* = 32, 5–13 years	CBT	CBT had higher reduction in pain scores compared to controls (86.6 vs. 33.3 %)
	RCS	•Psycho-education	No significant difference in pressure pain threshold
		•Cognitive and behavioral strategies	
		•Self-monitoring	
		Control group: SMC	
		4 monthly sessions	
		FU: 4 months	
Hicks et al. (2006)	*n* = 47, 9–16 years	CBT	CBT group had significant improvement in pain scores compared to controls (72 vs. 14 %) at 3-month follow-up
	RCS	•Relaxation	
	Recurrent headaches and abdominal pain	•Cognitive strategies (self-talk)	
		Control: SMC	
		Online and telephone sessions	
		FU: 3 months	
Robins et al. (2005)	*n* = 69, 6–16 years	CBT	Significantly less abdominal pain in the CBT group compared to controls. Benefit maintained at 1-year FU
	RCS	•Psycho-education	No significant difference in functional disability
		•Relaxation	
		•Coping strategies	
		Control : SMC	
		Five 50-min sessions	
		FU: 1 year	
Sanders et al. (1994)	*n* = 44, 6–12 years	CBT	Both groups reported significant decrease in pain
	RCS	•Parent contingency management	CBT group had lower relapse rate and higher rate of complete pain relief
		•Relaxation training	
		•Cognitive (self-talk)	
		Control: wait list	
		Six 50-min sessions	

(continued)

Table 38.3 (continued)

Article	Population and study design	Intervention/control	Outcome
Alfven and Lindstrom (2007)	$n=83$, 6–12 years	Group A	Pain improved in all groups
	RCS	•Psychological (psychoeducation) and physiotherapy (relaxation, breathing, coping skills)	Group C significantly better outcome (59 % decrease in pain scores)
		Group B	Group A and C had significantly decrease in tender points at 12 months
		•Physiotherapy only	
		Group C	
		•Integrated psychological and somatic therapy	
		Group D	
		•No treatment	
		Tender points (rated 0–8) assessed in all groups	
		FU: 12 months	
Groß and Warschburger (2013)	$n=29$, 7–12 years	CBT	CBT group significantly reduced pain and improved health-related quality of life compared to controls
	RCS	•Coping strategies	
		•Relaxation training	
		•Increasing self-esteem	
		Control: wait list	
		6 weekly group sessions	
		FU: 3 months	
van Tilburg et al. (2009)	$n=34$, 6–15 years	Home-based guided imagery	Treatment responders more in GI group compared to SMC (63.1 vs. 26.7 %)
	RCS	SMC	61.5 % of SMC patients responded to GI
		2 months treatment	Treatment benefit was maintained for 6 months
		FU: 6 months	
Gulewitsch et al. (2013)	$N=38$, 6–12 years	Hypnotherapy	55 % of hypnotherapy group in remission (>80 % improvement) vs. 6 % of controls and improved pain-related disability
	RCS	•Gut-directed hypnotherapy	Quality of life did not improve
		•4 weekly sessions	
		Control (no intervention)	
		FU: 3 months	
Vlieger et al. (2007/2012)	$n=53$, 8–18 years	Relaxation/hypnotherapy	Both groups had significant decrease in pain intensity and frequency
	RCS	•General relaxation	Decrease was more marked in hypnotherapy group compared to controls (85 vs. 25 %)
		•Gut-directed hypnotherapy	At mean 4.8 years follow-up ($n=49$), hypnotherapy still superior to controls (68 vs. 20 % in remission)
		•Ego-strengthening suggestions	Somatization scores also lower in hypnotherapy group long-term
		Control: SMC	
		Six 50-min sessions for 3 months	
		FU: 1 and 4.8 years	
Weydert et al. (2006)	$N=22$, 5–18 years	Guided imagery with progressive muscle relaxation	Significantly greater decrease in pain frequency and missed activities in GI group compare to controls (82 vs. 45 %) at 2-month follow-up
	RCS	Control: breathing exercises	
		Four weekly 60-min sessions	
		FU: 3 months	

(continued)

Table 38.3 (continued)

Article	Population and study design	Intervention/control	Outcome
Ball et al. (2003)	$n=11$, 5–18 years	Relaxation	Significant decrease in pain episodes. All patients randomized to wait list withdrew from the study
		•Abdominal breathing	
		•Progressive muscle relaxation	
		•Visualization	
		Control: wait list	
		Four sessions	
Wallander et al. (2011)	$n=63$, 11–17 years	Written self-disclosure + SMC	Intervention group with significant decrease in activity-limiting symptoms (50 % fewer days of pain in prior 2 weeks compared to controls) and reduced health care utilization
	RCS	•Three 20 min writing sessions	
		Control: SMC	
		FU: 6 months	
Humphreys and Gervitz (2000)	$n=64$, 4–18 years	Comparison between four randomized conditions	All groups reported reduction in pain. Fiber alone has 79 % reduction in pain reports, and fiber and relaxation have 100 % reduction in pain reports Addition of CBT and parent training has no additional benefit
	RCS	Fiber alone	Three psychological treatments had greater benefit compared to fiber alone (70.6 vs. 38.1 %)
		Fiber and relaxation	
		Fiber, relaxation, and CBT	
		Fiber, relaxation, CBT, and parent training	
		Eight-session duration not stated	

We have only included studies evaluating 10 or more children

RCS randomized controlled study, *IMC* intensive medical therapy, *SMC* standard medical therapy

FAP is controversial. A multicenter placebo-controlled study of 90 children with FAP, IBS, and functional dyspepsia compared the effect of 4-week amitriptyline therapy with placebo [87]. A total of 63 % of patients reported feeling better in the amitriptyline group compared with 57.5 % in the placebo group. None of the outcome variables were significantly different between the two groups. A fixed dose for a relatively short period of time was used in this trial. Future studies evaluating the effect of an escalating dosage schedule for a relatively longer period of time would help to clarify the role of tricyclic antidepressants in the treatment of FAP.

Cyproheptadine is a first generation antihistamine commonly used in younger children with FAP. It is also used for migraine prevention and has antiserotonergic and anticholinergic properties. In a smaller study of 29 children (4.5–16 years) with FAP, cyproheptadine (0.25–0.5 mg/kg/day) for 2 weeks improved pain frequency, intensity, and global health (87 % of cyproheptadine vs. 36 % of controls; $p=0.005$) [88].

Another study evaluated citalopram, a selective serotonin reuptake inhibitor, in 25 children with FAP aged 7–18 years. In this flexible-dose, open-label trial, the initial daily dose of citalopram was 10 mg for a week, increasing to 20 mg at week 2 and then 40 mg at week 4 if there was no clinical response and the medication was well tolerated. Total duration of treatment was 12 weeks [89]. The primary outcome measure was Clinical Global Impression Scale-Improvement. Secondary outcome measures included self- and parental reports of abdominal pain, anxiety, depression, somatic symptoms, and functional impairment. Eighty-four percent of patients were classified as responders in whom the abdominal pain rating, anxiety, depression, and functional impairment all improved significantly. It is not clear if the primary beneficial effect of selective serotonin reuptake inhibitor therapy in FAP is through modulation of brain regions involved in visceral sensation or due to their effect on psychiatric comorbid symptoms. A more recent placebo-controlled study evaluated the efficacy of citalopram 20 m daily for 4 weeks in 86 children (6–18 years) with FAP. Only a trend toward effectiveness of citalopram was noted at 12 weeks (72 % vs. 53 % response rates in citalopram vs. controls; $p=0.059$). Notably, there were no differences in anxiety, depression, or somatization scores between the two groups [90].

Low-grade bowel inflammation and immune alteration have been reported in adults with IBS and are associated with changes in the gut flora. In post-infectious IBS patients, probiotics can help to restore the qualitative and quantitative changes in indigenous gut flora and improve symptoms [12]. Lactobacillus GG therapy for 4 weeks was compared to placebo in 104 children with FAP, functional dyspepsia, or IBS [91]. Twenty-five percent of children in the Lactobacillus GG

group compared to 9.6% in the placebo group had improvement in abdominal pain. In this study, children with IBS were more likely to respond to Lactobacillus GG therapy compared to children with FAP. Another study compared 8-week *Lactobacillus rhamnosus* GG therapy in 141 children with IBS syndrome and FAP with placebo [92]. At week 12, improvement in abdominal pain was achieved in 72% subjects in the probiotics group compared to 53% in the placebo group. A recent meta-analysis including three trials on *Lactobacillus rhamnosus* GG found moderate improvement in pain intensity among children with pain-associated FGIDs [93] Also, treatment with *Lactobacillus reuteri* for 4 weeks demonstrated efficacy in improving pain intensity ($p<0.001$) but not frequency in children with FAP compared to controls [94]. Probiotics may thus be helpful in treating children with pain-associated FGIDs, but their mechanisms of action are not well understood. Modulation of gastrointestinal lumen toward an anti-inflammatory state and conversion of undigested carbohydrates into short-chain fatty acids may help to improve gut function.

Outcome

The relationship between FAP and FGIDs in adult life is controversial. A weak association between FAP in childhood and headaches and IBS in adult life has been suggested [95]. A recent meta-analysis of 18 studies that included 1331 children with FAP who were followed for a median of 5 years, 29.1% continued to report abdominal pain at follow-up [96]. Chitkara et al. reported that 18–61% of children with FAP continue to report symptom of abdominal pain 5–30 years later [9]. The risk factors associated with poor prognosis include onset of symptoms before 6 years of age, duration of symptoms more than 6 months, family history of pain-related FGIDs, multiple surgical procedures, low educational level, and socioeconomic status [97, 98]. Mulvaney et al. identified higher levels of anxiety, depression, lower self-worth perception, and more negative life events in subjects who had poor outcome at 5-year follow-up [66].

Summary

Functional abdominal pain is one of the most common FGIDs of childhood. Since there are no identifiable structural abnormalities of the GI tract and no diagnostic tests to evaluate alterations in GI function in FAP, it is primarily a clinical diagnosis. Development of symptom-based criteria has helped in clinical decision-making; however, further work is required to validate their accuracy in a clinical setting. Psychological comorbidities, functional disability, and parental perception of the severity of their child's illness have important bearing on treatment outcome. Recent data suggest that psychological therapy is effective in the vast majority of children and is likely to emerge as the first-line treatment for FAP in the coming years. Medication and dietary alterations serve as useful adjuncts to psychological treatment.

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Cyclic Vomiting Syndrome: Comorbidities and Treatment

39

B.U.K. Li and Katja Kovacic

Cyclic vomiting syndrome (CVS) diagnosis has been facilitated by the recently defined consensus diagnostic criteria by NASPGHAN (2008), Rome III (2006), Rome IV (2016), and International Headache Society (2013) criteria. This chapter focuses on the most recent data on comorbidities and clinical subphenotypes, pathophysiologic pathways, and new therapeutic avenues.

Despite improved characterization, recognition, and understanding of CVS in the past two decades, without a delineated pathophysiologic cascade, it remains classified as a functional gastrointestinal disorder (Table 39.1). Although originally perceived to be a pediatric disorder, the past decade has been witness to a dramatic rise in diagnosed adults. In both children and adults, the hallmark symptoms described by Samuel Gee in 1882 remain applicable today and include stereotypical, severe episodes of vomiting punctuating symptom-free periods, or baseline health [1]. Recent work has begun to expand the list of comorbidities and clinical subphenotypes and identify pathophysiologic pathways and new therapeutic avenues.

Definition

Earlier clinical diagnosis has been facilitated by the recently defined consensus diagnostic criteria by NASPGHAN (2008) and Rome III (2006) criteria, the former being quantitatively more rigorous, i.e., requiring 3–5 vs. 2 total episodes [2] (Table 39.2). There is common confusion over the nomenclature as the older classification is "abdominal migraine" and the newer term since the 1990s is "cyclic vomiting syndrome" or "cyclical vomiting syndrome" (UK). Today, from an operational standpoint, the predominant and most consistent symptom during episodes defines the illness, i.e., abdominal pain is termed abdominal migraine, and conversely vomiting is denoted CVS. However, there is considerable clinical overlap because ~50 % of those diagnosed with abdominal migraine also vomit, and 80 % of those with CVS also have abdominal pain.

The continuum between CVS and migraine was suggested by Whitney in 1898 and corroborated by other authors including us in 1998 [3, 4]. In a cross-sectional school survey in Scotland, Abu-Arafeh described a developmental progression from CVS to abdominal migraine and migraine headaches, median ages 5, 9, and 11 years with prevalences of 1.9 %, 4 %, and 11 %, respectively [5]. This suggests a natural history that begins with CVS and ends with migraines. Although some experience all three phases, the largest group trades CVS for migraines by age 10. We estimate 75 % will develop migraine headaches by age 18 years (Li, unpublished data).

The previous lack of a specific ICD 9 code has rendered it difficult to establish the true prevalence of CVS. However, ICD 10 now includes a specific code (G43.A0) specific for CVS [6]. Typical misdiagnoses, including gastroenteritis, gastroesophageal reflux, food poisoning, and eating disorders, often delay accurate diagnosis by a median 2.5 years [7, 8]. At our GI clinic, CVS was second only to gastroesophageal reflux as a cause of recurrent vomiting [9]. Two school-based surveys estimated the frequency to be 2 % in Scottish and Turkish children (Table 39.3) [5, 10], and the incidence of new cases of CVS was reported to be 3.15 per 100,000 children per year in Irish children. In our series, the average age of onset of CVS is 4.8 years with predominance in girls over boys (57:43). Similar data was replicated in a large study from Iran [8].

Impact on QOL

CVS has a significant deleterious impact on the quality of life in affected children. Although well in between episodes approximately 90 % of the time, 58 % of affected children require intravenous fluids during episodes and average ten visits to the emergency

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department. School-age children miss an average of 24 days of school per year [7, 11]. Medical morbidity is reflected by the high average annualized cost of management of $17,000 in 1998 that includes doctor visits, emergency department visits, inpatient hospitalizations, missed work by parents, and biochemical, radiographic, and endoscopic testing [12]. A growing number of comorbid conditions such as anxiety and postural tachycardia syndrome (POTS) also contribute to functional disability. We have documented lower global quality of life scores than in healthy controls and those with functional GI disorders (irritable bowel syndrome) and equivalent to organic GI diseases (e.g., inflammatory bowel disease, gastritis, fatty liver disease) [13]. Nearly half (47 % overall, 59 % of school age children) of CVS sufferers meet criteria for an anxiety disorder and we found that anxiety was the prime predictor of impaired quality of life, even more than the quantitative severity of episodes [14].

Pathophysiology

In the absence of a defined etiopathogenesis, CVS remains classified as an idiopathic disorder. Recent investigations support the contributory roles of mitochondrial DNA (mtDNA) mutations and dysfunction, heightened hypothalamic–pituitary–adrenal (HPA) axis activation, and autonomic nervous system (ANS) dysfunction. CVS is a functional brain–gut disorder perhaps mediated through altered brainstem modulation of effector signals.

Table 39.1 Functional nausea and vomiting disorders

Functional dyspepsia
Functional nausea (pediatric Rome IV criteria)
Functional vomiting
Cyclic vomiting syndrome
Rumination syndrome
Aerophagia

Mitochondrial Dysfunction

In two series, a striking maternal inheritance pattern was recognized for migraines in 64 % and 54 % of probands with CVS [15, 16]. Evidence of mitochondrial dysfunction was first provided using NMR spectroscopy to establish decreased ATP production in peripheral muscle in migraineurs [17]. This mitochondrial pathogenesis gained substantial support following the recent identification of two tandem mtDNA polymorphisms, 16519T, and 3010A with impressive odds ratios of 17 and 15 in CVS and migraine in haplotype H, respectively [18]. Because the mutations are found in the control region rather than the enzyme sequence, the structure-to-function relationship is unclear. However, elevated lactates, ketones, and Krebs cycle intermediates during attacks are consistent with mitochondrial dysfunction. In addition, small therapeutic trials show promising effects of mitochondrial supplements coenzyme Q10, L-carnitine, and riboflavin in the treatment of migraines and CVS [19–22].

These two mtDNA mutations are also found in depression, chronic fatigue, and irritable bowel syndrome and may link these clinical comorbidities together to a common mitochondrial susceptibility factor [23].

Table 39.2 NASPGHAN, Rome III, and Rome IV diagnostic criteria

NASPGHAN
1. At least five attacks in any interval or a minimum of three attacks during a 6-month period
2. Episodic attacks of intense nausea and vomiting lasting 1 h to 10 days and occurring at least 1 week apart
3. Stereotypical pattern and symptoms in the individual patient
4. Vomiting during attacks occurs at least 4 times/h for at least 1 h
5. Return to baseline health between episodes
6. Not attributed to another disorder
Rome III
1. Two or more periods of intense nausea and unremitting vomiting or retching lasting hours to days
2. Return to usual state of health lasting weeks to months
Rome IV
Must include all of the following
1. The occurrence of 2 or more periods of intense, unremitting nausea and paroxysmal vomiting, lasting hours to days within a 6-month period
2. Episodes are stereotypical in each patient
3. Episodes are separated by weeks to months with return to baseline health between episodes
4. After appropriate medical evaluation, the symptoms cannot be attributed to another condition

All respective criteria must be met to meet consensus definitions for both NASPGHAN, Rome III and Rome IV (see Benninga et al.: http://www.ncbi.nlm.nih.gov/pubmed/27144631 Or [if !supportLists]2- [endif]Hyams et al.: http://www.ncbi.nlm.nih.gov/pubmed/27144632.)

Table 39.3 Epidemiology and demographics

Features	
Age of onset	4.8 years
Delay in diagnosis	2.5 years
Prevalence	2 %
Incidence	3.15/100,000
Female/male	57:43
Migraine association	39–87 %

Adapted from Li BUK, Balint J. Cyclic vomiting syndrome: evolution in our understanding of a brain–gut disorder. In: Advances in Pediatrics. Mosby, 2000: 117–160, with permission

HPA Axis Activation

Stressors, both psychological (excitement, panic) and physical (fever, lack of sleep), are common triggers of attacks of CVS. Activation of the HPA axis during episodes of CVS was first described by Wolfe, Adler, and later Sato, manifested by elevated levels of adrenocorticotropic hormone (ACTH), antidiuretic hormone, cortisol, catecholamines, and prostaglandin E2 and hypertension [24, 25]. Increased vasopressin levels are also described in a recent case report [26]. Attenuation of CVS symptoms occurred after use of high-dose dexamethasone by Wolfe and Adler and indomethacin and clonidine by Sato et al. [27].

The role of corticotropin-releasing factor (CRF) as a brain–gut neuroendocrine mediator of foregut motility has been extensively described in animals by Taché et al. [28]. In response to stressors, released CRF from the hypothalamus stimulates inhibitory motor neurons in the dorsal motor nucleus of the vagus and causes delayed gastric emptying, independent of downstream effects of ACTH and cortisol secretion. In animals, psychological (water avoidance) and physical (cytokine IL-1β) stressors can impair foregut motility. Ongoing investigation of the pathophysiologic role of CRF in CVS may open a potential therapeutic avenue using CRF antagonists. Also, tricyclic antidepressants, which inhibit the promoter activity of the CRF gene, are the most efficacious agents in treating CVS. Recent gene sequencing data found that a significant number of pediatric CVS sufferers carry a mutation in a stress-sensitive calcium channel (RYR2 gene) influencing the autonomic nervous system [29]. Although speculative, this data may support involvement of stress-induced calcium release in neuronal mitochondria, which in turn may cause autonomic dysregulation.

Autonomic Dysfunction

Most of the prominent symptoms of CVS are expressed through the ANS. The peripheral vasoconstriction, hypersalivation, diaphoresis, tachycardia, and listlessness are in fact prominent manifestations of nausea that persist throughout the episode typically unrelieved by evacuation of the stomach. Autonomic dysfunction in the form of POTS was reported in 47 % of children with CVS by Chelimsky [30]. They noted that treatment of POTS appeared to help reduce the frequency of CVS episodes. We found an overall POTS prevalence of 19 % in our CVS patients, and when we limited the cohort to adolescents >11 years in whom POTS is known to be more common, the rate was 31 %. Formal investigation of the ANS function in children and adults with CVS reveals a consistent pattern of heightened sympathetic tone and normal parasympathetic tone [30]. This imbalance is also described in migraines and other functional gastrointestinal disorders [31].

A Model

How these pathophysiologic pathways fit together in a comprehensive model remains to be delineated. mtDNA mutations may impair cellular energy production when needs are increased during psychological or physical stress conditions. If the production cannot meet the heightened demands, autonomic neurons may be the target because of their high intrinsic energy demands. CRF may be the initiating signal triggered by psychological or physical stressors that inhibit the upper GI tract motility. The penultimate defect in CVS that allows the emetic motor program to feed forward and continue for hours even despite evacuation of all gastric contents has been hypothesized to be in the periaqueductal gray area [32]. This area modulates brain-to-peripheral ANS signals such as the emetic motor program mediated by the vagus.

Clinical Patterns

CVS has a distinctive on–off temporal pattern of vomiting that serves as an essential criterion for diagnosis. CVS is distinguished by the "on" pattern of discrete, recurrent, and singularly severe episodes of vomiting that are stereotypical within the individual as to time of onset (usually early morning), duration (hours or days), and symptomatology (pallor, listlessness). The "off" pattern is week- or month-long intervals when the child resumes completely normal or baseline health (e.g., if there is other chronic disease), although 5–12 % may have interepisodic symptoms of nausea and mild vomiting [7]. This particular persistent interictal pattern has been labeled "coalescent" CVS although the daily nausea and vomiting is usually less severe than that during the CVS episodes themselves. During the episodes, the most common symptoms are listlessness (93 %) and pallor (91 %), and others include low-grade fever or hypothermia, intermittent flushing, diaphoresis, nausea, drooling, diarrhea, and hypertension in the Sato variant. Although found in significantly higher frequency than in patients with other GI

disorders, fewer than half have classic migraine features of headache, photophobia, and phonophobia.

The duration of episodes generally ranges from hours to days with a median duration of 27 h. A study of Iranian CVS children found a mean duration of 4.3 days [8]. Episodes can last as long as 10 days but are generally self-limited. Half of patients have "cyclic" intervals most commonly 4 weeks, predictable within a week, and half have "sporadic," unpredictable attacks. The most common time of onset is early morning (2–4 a.m.) or upon awakening (6–8 a.m.) in 42 %. Many have a remarkably rapid onset (1.5 h) and denouement (6 h) from the last emesis to the point of being able to eat and be playful. The 67 % with a prodrome experience pallor, diaphoresis, abdominal pain, and headache before the onset of vomiting but rarely visual disturbances of a migraine aura.

The vomiting in CVS is uniquely rapid fire and peaks at a median frequency of six times an hour and 15 times per episode (Table 39.3). The vomiting is typically forceful and contains bile, mucus, and occasionally blood, the latter usually the result of prolapse gastropathy. The intense nausea differs from that in gastroenteritis or bowel obstruction in that it persists even after complete evacuation of gastric contents as if independent of gastric feedback, presumably centrally driven. In fact, many adolescents describe it as the most distressing symptom, only relieved during sleep. Due to the unrelenting nausea, during episodes, these children appear much more debilitated when compared to those with gastroenteritis, often curled into a fetal position, listless, and withdrawn to the point of being unable to walk or interact. Anorexia, nausea, midline abdominal pain, and retching are the most common gastrointestinal symptoms.

Certain unusual behaviors can be observed during CVS episodes that can raise questions about an underlying psychiatric disorder. There are children who drink compulsively and then vomit and describe that this maneuver dilutes the bitter bile and aids in its evacuation. Others take prolonged, scalding hot showers or baths until the hot water supply is exhausted. In adults with CVS, this unique symptom is also associated with chronic, high dose marijuana use and termed "cannabinoid hyperemesis syndrome" [15]. Nearly all turn their rooms into a darkened cave in order to avoid lights and sounds that trigger more nausea. Many are hyperesthetic to motion, odor, taste, and even parental touch and attempt to shut out the external environmental stimuli that often trigger more nausea and vomiting.

Various recurring stressors are recognized to precipitate CVS episodes in 76 % of patients. These include psychological (44 %), infectious (31 %), and physical triggers [7]. The psychological stress is more often of an excitatory nature such as holidays, birthdays, outings, and vacations such as at Disney World. Episodes may be triggered by various infections including upper respiratory infections, sinusitis, strep throat, and influenza. Dietary triggers include aged-cheese, chocolate, monosodium glutamate, and fluctuating caffeine intake (23 %). Lack of sleep from excess physical exhaustion from travel, sports, sleepovers or a sleep disorder (24 %), and menses (catamenial CVS—22 %) are also common inciting events. Environmental triggers include changes in barometric pressures in weather fronts. One subgroup with a precisely timed interval every 60 days (predictable within a week) with no identifiable triggers is especially refractory to therapy.

Comorbidities

The evolving clinical picture of CVS has included an increasing number of associated comorbidities. In Boles' series, 25 % had coexistent neurological findings of developmental delay, seizures, hypotonia, and skeletal myopathy as well as cognitive and cranial nerve dysfunction [33]. These children classified as CVS+ were found to have an earlier age of onset for CVS and a three- to eightfold higher prevalence of dysautonomic (neurovascular dystrophy) and constitutional (growth retardation) manifestations than CVS patients without neurological findings. Other comorbidities in non-neurologically impaired children include anxiety (47 %) and depression (14 %) [34], irritable bowel syndrome (67 %) [35], GERD (39 %), colonic dysmotility (20 %) [33], limited stamina or chronic fatigue (52 %) (Li, unpublished), sleep disturbance (onset or maintenance) (48 %) (Leung, Li, unpublished), POTS (19 %) (Leung, Li, unpublished), and complex regional pain syndrome (12 %) [36]. Often, these contribute to the poor quality of life and have to be treated concomitantly to help restore the child to functionality.

Subgroups

There appear to be subphenotypes of CVS, some of which overlap and may be present in the same patient. The 83 % that are migraine related (positive family or personal history) tend to have significantly less severe episodes that are more responsive to antimigraine therapy [37]. It now appears that the majority has a matrilineal inheritance pattern (for migraine and other functional disorders) and may have mtDNA single nucleotide polymorphisms and mitochondrial dysfunction [16]. Many appear to have predominantly sympathetic overtone and comorbid POTS in whom treatment of POTS helps reduce frequency of vomiting episodes. The Sato variant is associated with hypertension during episodes and an endocrine profile of heightened HPA axis activation. Those with long-interval calendar-timed episodes every 60+ days apart appear particularly difficult to treat. Boles has described a group with neurodevelopmental deficits in whom CVS begins early in life [33]. There are post-menarcheal girls with catamenial CVS who respond to low-estrogen birth control pills or ablation of menses.

A group of young adult males (>100 case reports) who use large amounts of recreational or medical marijuana over several years may in fact trigger CVS symptoms that have been labeled as cannabis-induced hyperemesis. However, it is more likely cannabis-triggered CVS [38]. Several series reports termination of bouts of emesis after cessation of chronic use of marijuana. Another case series and a large, anonymous survey of CVS indicate that marijuana users experience reduction in nausea and anxiety raising the possibility that marijuana may aggravate symptoms in some and mitigate them in others [39].

Evaluation

At present, there are no specific tests to diagnose CVS, and the diagnosis rests primarily upon fulfilling clinical criteria. The first step requires differentiating a cyclic or sporadic pattern (high intensity, low frequency) of vomiting in which extraintestinal disorders including CVS are most common from a chronic vomiting (low intensity, high frequency, e.g., daily) one in which upper GI tract disorders predominate [9]. Approximately 90 % of children who fulfill the NASPGHAN consensus criteria (Table 39.2) are ultimately found to have CVS [2, 9]. Most of the testing in undiagnosed children who present with recurrent vomiting is directed toward identifying underlying gastrointestinal, neurologic, renal, metabolic, and endocrine causes that can be discovered in the remaining 10 %. The challenge to the clinician is to determine which and how much testing should be performed, as the traditional "shotgun" approach is costly, time-consuming, and invasive.

The recent NASPGHAN Consensus Statement (2008) guidelines recommend against the traditional shotgun evaluation and for initial an upper gastrointestinal series to exclude malrotation and anatomic obstructions and a basic metabolic profile (electrolytes, glucose, BUN, creatinine) [2]. Further testing beyond that should be based upon specific warning signs (Table 39.4). In those who present with bilious vomiting and abdominal tenderness, abdominal imaging should be performed to exclude hydronephrosis, pancreatitis, and cholecystitis. In those in whom episodes are triggered by intercurrent illnesses, fasting, or high-protein meals, screening should be performed for urea cycle, fatty acid oxidation, disorders of organic and amino acid metabolism, and mitochondrial disorders. This screening has a better diagnostic yield in the early part of an episode of CVS before intravenous glucose and fluids are administered. Those presenting with abnormal neurological findings including altered mental status, papilledema, ataxia, or seizure should have a neurological evaluation and brain MRI considered. Presentation of CVS under the age of 2 should also prompt further metabolic or neurological testing [2].

Treatment

Management of CVS is multifaceted and challenging. The goals of treatment are to reduce the frequency and severity of episodes, reduce school absenteeism and enhance functionality, improve quality of life, and establish a protocol for rescue therapy in home and in hospital. Treatment of nausea and vomiting, abdominal pain, and dehydration during acute episodes requires a protocol for use at home, emergency departments, and hospital wards. Lifestyle modifications, similar to those in migraines, during the well phase can help prevent episodes and are discussed below. For those with more frequent or severe episodes (e.g., more than once a month), prophylactic therapy taken daily to prevent the next episode is warranted. In some with less frequent or severe episodes, abortive therapy taken only during the prodrome or at the onset of the episode is recommended. The use of mitochondrial supplements to treat suspected underlying mitochondrial dysfunction is gaining evidence and acceptance.

At present, there are no controlled therapeutic trials. One formal randomized controlled trial on IV ondansetron was attempted by the authors and thwarted by an impressive 90 % reduction in rate of episodes upon enrollment even without prophylactic therapy (Li, unpublished data). The NASPGHAN Consensus Statement therapeutic recommendations are based upon results from case series and expert opinion of the task force [2]. The main recommendations include first-line prophylactic use of cyproheptadine and amitriptyline in children under age 5 years and 5 years or older, respectively, with propranolol as the second line. Sumatriptan was recommended as an abortive agent for

Table 39.4 Evaluation of cyclic vomiting

• Patient meets consensus criteria for CVS UGI series to evaluate for malrotation + serum electrolytes, BUN, creatinine and no warning signs or findings to suggest an organic disorder → trial of empiric therapy to treat CVS
If warning signs are present
• Severe abdominal pain, bilious, and/or hematemesis → liver and pancreatic serum chemistries, abdominal ultrasound (or CT or MRI), esophagogastroduodenoscopy
• Fasting, high-protein meal, intercurrent illness precipitating episodes of vomiting → serum and urine metabolic evaluation (lactate, ammonia, carnitine profile, amino acids, and organic acids) *prior to treatment during episode and metabolic consult*
• Abnormal neurological findings (altered mental status, papilledema) → brain MRI, neurology consult

those >12 years. For rescue therapy during acute episodes, IV rehydration with high-dose antiemetic ondansetron (0.3–0.4 mg/kg/dose) and sedation from diphenhydramine or lorazepam was recommended.

Rescue Approach

The rescue therapies are used when the vomiting is well established in an episode and fails to respond to abortive strategies. The goal is to correct fluid and electrolyte deficits and render the child more comfortable through antiemetic therapy, analgesics, and sedation for relief from unrelenting nausea, vomiting, and pain. The recommendation is for an IV bolus of saline for rapid correction of fluid deficits and 10% dextrose 0.45 normal saline at 1.5× maintenance rates to provide sufficient cellular energy to terminate ketosis. Poor response to IV therapy and progressive lethargy should prompt evaluation for hyponatremia from high vasopressin levels and water overload [26]. One may have to reduce IV rates and increase Na^+ content in the face of hyponatremia and diminished urine output resulting from elevated antidiuretic hormone release especially in the Sato-variant CVS. Ondansetron has been the most widely used $5HT_3$ antagonist given safely at higher than standard doses (0.3–0.4 mg/kg/dose) [15]. Diphenhydramine, lorazepam, or chlorpromazine combined with diphenhydramine are used for sedation as this may be the only means of providing relief from the unrelenting nausea and pain (Table 39.5). When the first-line analgesic ketorolac fails to alleviate pain, hydromorphone can be used and is occasionally required as a continuous patient-controlled analgesia. In cases refractory to aggressive IV therapy, the sedative dexmedetomidine may be considered under close monitoring in an intensive care unit to provide deep sedation, analgesia, and anxiolysis. Experience with this therapy rests on case reports and needs careful consideration of side effects [40].

Lifestyle Modifications

Lifestyle modifications are used during the interictal phase of CVS when the child is not in an episode in order to avoid exposure to known and potential precipitants of episodes. The lack of sleep resulting from disturbed sleep patterns, sleepovers, or travel sports tournaments are often cited as triggers of episodes. Good sleep hygiene (e.g., turning off all phones, computers, music, TV) with a regimented sleep time can help reduce the frequency of episodes. Providing at higher than maintenance fluid intake is widely used to treat migraines and POTS. Providing energy sources before strenuous activity, preferably of low glycemic index and high-protein sources, may prevent an energy deficit. Routine exercise can help reverse the deconditioned state. Finally, avoiding identified triggers specific to the individual (e.g., lack of sleep) or generally found in migraines (monosodium glutamate and fluctuations in caffeine intake) may help reduce the frequency of episodes. In some, extending sleep by modifying the school start time past 9:00 am has reduced the frequency of episodes. Fleisher reported that consultation, education, and reassurance ("good doctor effect," perhaps relieving anxiety) alone reduced the frequency of episodes in 70% of patients without beginning prophylactic therapy [35].

Prophylactic Therapy

Prophylactic therapy is administered during the interictal period in order to prevent future episodes. The NASPGHAN consensus recommendations for the initial treatment were for cyproheptadine for the younger (<5 years) and amitriptyline for the older children and adolescents (≥5 years) [2] (Table 39.6).

Table 39.5 Abortive and rescue pharmacotherapy

Antimigraine
Sumatriptan 20 mg intranasal at episode onset and may repeat once or 25 mg po once vs. 3–6 mg s.c. once SE: chest and neck burning, coronary vasospasm, headache
Alternatives: *Rizatriptan*, *Zolmitriptan*, *Frovatriptan* (*longer half life*)
Antiemetic
Ondansetron 0.3–0.4 mg/kg per dose (≤12 mg) q 4–6 h iv/po/rectal/topical. SE: headache, drowsiness, dry mouth
Alternatives: *Granisetron*
Aprepitant 3 day regimen: 125, 80, 80 mg one q.d. prior to anticipated episode
Fosaprepitant 115 mg IV day one (aprepitant day 2–3)
Sedative
Lorazepam 0.05–0.1 mg/kg per dose q 6 h iv/po: useful adjunct to ondansetron. SE: sedation, respiratory depression
Chlorpromazine 0.5–1 mg/kg per dose q 6 h iv/po. SE: drowsiness, hypotension, seizures
Diphenhydramine 1.25 mg/kg per dose q 6 h iv/po: useful adjunct to chlorpromazine. SE: hypotension, sedation, dizziness
Dexmedetomidine bolus 0.5 mcg/kg over 15 min → 0.5mcg/kg/h (up to 1.5 mcg/kg/h) continuous infusion
Analgesic
Ketorolac 0.5–1 mg/kg per dose q 6 h iv/po. SE: gastrointestinal bleeding, dyspepsia
Alternatives: opioids (hydromorphone)

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Despite its pharmacokinetics, cyproheptadine (0.25–0.5 mg/kg) appears to be effective given as a single nighttime dose, rather than in two or three divided doses [41]. Amitriptyline causes side effects in 50 %, the most common being morning sedation (like a hangover), and is stopped in 21 % [42]. Beginning at a low dosage of 0.2–0.3 mg/kg at bedtime and titrating in 10 mg increments every week (unless too sedated) to the target dose of 1.0–1.5 mg/kg allows the child to adapt to the side effects. Switching to other tricyclic antidepressants (TCA) such as nortriptyline and desipramine may circumvent intolerable side effects. An EKG for QTc interval is recommended before starting amitriptyline and after reaching the target dose to monitor for prolonged QTc interval [43]. Impaired drug metabolism in those with CYP2D6 and CYP2C19 deficiency promotes TCA toxicity at low doses. Conversely rapid metabolizers may require higher than usual TCA dosing guided by blood levels [44]. Propranolol is second line and can be monitored for efficacy and toxicity by an expected drop in pulse rate of 15–20 beats per minute and drop below 55 bpm, respectively. A recent large prospective study reported high efficacy of the prokinetic erythromycin for 7 days in conjunction with propranolol compared to propranolol alone in aborting episodes (90 % vs. 77 %, respectively) [45]. New retrospective data on the NK-1 receptor antagonist aprepitant show promising results for this agent both prophylactically (twice weekly) and as an abortive agent if given during prodrome [46].

If standard prophylactic therapy fails, anticonvulsants and Ca^{2+}-channel antagonists have been used. Phenobarbital at low (2–3 mg/kg) nighttime doses has been reported to be effective [47]. In children, cognitive dysfunction is a well-known side effect and one that occurs with other anticonvulsants as well. Others used topiramate, zonisamide, and levetiracetam, with positive evidence in adults with migraine headaches and cyclic vomiting syndrome [48, 49]. Another group of agents includes Ca^{2+}-channel antagonists with the main side effect of hypotension.

Treatment by Subgroup

Treatment may be selected by clinical subgroup. Children with so-called migraine related with a positive family history or migraines themselves are much more likely to respond to antimigraine agents such as cyproheptadine, amitriptyline, and propranolol (79 % vs. 36 %) than those children without a migraine connection [37]. Post-menarcheal girls with catamenial CVS often respond to low-estrogen birth control pills (Loestrin, Lo/Ovral, Alesse, Seasonale) or Depo-Provera. Sato-variant CVS associated with intraepisode hypertension have been treated with tricyclic antidepressants in the USA and valproic acid in Japan [19].

Abortive Therapy

Abortive therapy is given during the prodrome or at the beginning of the vomiting episode in the hope of stopping it. The most specific abortive therapy includes antimigraine triptans. The nasal (sumatriptan or zolmitriptan) or subcutaneous (sumatriptan) forms appear more effective than oral forms that cannot effectively reach the duodenum due to repeated vomiting (Table 39.5) [2, 50–52]. The triptans appear to be either fully effective or not at all and more effective if administered early in episode and if the duration of episodes is less than 24 h (Li, unpublished data). They may also be effective in the absence of a migraine history [51].

In a few children, ondansetron given alone aborts episodes in progress. Although the oral forms may not reach

Table 39.6 Prophylactic pharmacotherapy

Antimigraine
Amitriptyline start and 0.2–0.3 mg/kg and advance to 1–1.5 mg/kg/day q.h.s.: monitor EKG QTc interval prior to starting. First choice ≥5 years old. Side effects: sedation, anticholinergic
Propranolol 0.25–1 mg/kg/day divided b.i.d or t.i.d: monitor resting heart rate. SE: hypotension, bradycardia, fatigue
Cyproheptadine 0.25–0.5 mg/kg/day divided b.i.d. or q.h.s.: First choice <5 years old. SE: sedation, weight gain, anticholinergic
Alternatives: *nortriptyline*, *desipramine*, *doxepin*
Anticonvulsants
Topiramate titrate to 1.5–2.0 mg/kg/day divided b.i.d.
Phenobarbital 2–3 mg/kg/day q.h.s. SE: sedation, cognitive impairment
Alternatives: *gabapentin*, *levetiracetam*, *zonisamide*, *valproate*, *carbamazepine*
NK-1 receptor antagonist
Aprepitant 125 mg PO twice weekly (>60 kg); 80 mg (40–60 kg); 40 mg (<40 kg)
Mitochondrial supplements
L-*Carnitine* 50–100 mg/kg ≤ 2 g/day divided b.i.d. SE: diarrhea, fishy body odor
Coenzyme Q_{10} 10 mg/kg/divided b.i.d. ≤600 mg/day
Riboflavin 10 mg/kg/day divided b.i.d. ≤400 mg/day

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to duodenum, ondansetron can be reformulated by individual pharmacies into a rectal suppository or topical forms. Although not established, we use the same dose as the oral form. In a few adolescents with severe, disabling abdominal pain accompanying the vomiting, use of opioids such as hydromorphone can quickly abolish the pain and ensuing vomiting. The NK1 antagonist aprepitant may be given orally during the prodrome or prior to the anticipated vomiting during calendar-timed CVS episodes [46].

Mitochondrial Supplements

The use of mitochondrial supplements as adjunctive prophylactic therapy in CVS is being used more and more based upon evidence in migraines. Their use in suspected mitochondrial dysfunction has been bolstered by the recent finding of two mitochondrial DNA mutations by Boles [19]. In some children, the accompanying chronic fatigue may respond to these supplements. These supplements have demonstrated efficacy in prevention of migraine headaches in adults (randomized controlled trial) and preliminary evidence of efficacy in pediatric migraine and CVS in children [53–55]. The doses used include riboflavin at 10 mg/kg divided b.i.d. to 400 mg/day, L-carnitine at 50–100 mg/kg up to 2 g/day divided b.i.d., and CoQ10 10 mg/kg up to 400 mg/day divided b.i.d. The dose and duration of therapy has not been established in children with CVS. Acupuncture using P6 point has also been used with variable efficacy [56].

Approach to the Refractory or Disabled Patient

In tertiary and quaternary referral settings, a sizeable number of children with CVS do not respond to the therapies outlined above. There are several approaches we have used in such patients. The first is to reinvestigate the possibility of a specific precipitating factor(s) that can be addressed. In our experience the most common is a family- or school-related psychological stressor or intense anxiety in the child that leads to academic disability (school absenteeism) and requires a psychologist for diagnosis and treatment. If the child or adolescent cannot be progressively reintegrated to school, referral to an intensive rehabilitation program may be required to restore functionality. Some have been diagnosed with intractable chronic sinusitis that fails to respond to standard antibiotic and decongestant therapy and requires otolaryngological intervention. The second is to reconsider the diagnosis of CVS and whether there is a specific underlying organic cause. Identified surgical diagnoses found upon retesting in episodic vomiting include volvulus from malrotation, acute hydronephrosis, and subtentorial tumors (e.g., Chiari malformation). For example, it may be prudent to obtain an abdominal ultrasound *during* the episode to determine if acute hydronephrosis was missed during a screening ultrasound when not in an episode.

If no specific trigger or cause can be identified and prophylactic monotherapy fails to reduce the frequency and severity of episodes, combination therapy has been anecdotally successful. Amitriptyline can be combined with propranolol, topiramate, or phenobarbital in children refractory to single agent therapy.

In children with prolonged episodes longer than 5 days who continue to have severe and debilitating nausea and vomiting despite therapy, induced sleep may be the only rescue option. In fact, 72 % of the children in our series report sleep as the harbinger of the end of the episode. We have observed that induced sleep will sometimes end the episode, seemingly as if the "vomiting center" in the brainstem has "rebooted" back to baseline in the off position. The consensus recommendation is either intravenous lorazepam or chlorpromazine with diphenhydramine [2]. However, if both fail to sedate and ameliorate the unrelenting nausea and vomiting, general anesthesia may be the last resort. In one small case series, 18 h of dexmedetomidine-induced general anesthesia terminated prolonged, intractable episodes in three children [40]. Although this protocol required continuous monitoring in the PICU, because of its lack of respiratory depression it does not require intubation. We have also used this approach successfully in extreme cases.

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Aerophagia

40

Carlo Di Lorenzo

Aerophagia is a functional gastrointestinal disorder that is commonly diagnosed in children of any age. Its severity may range from a mere nuisance to an embarrassing and debilitating condition. The pathophysiology of this condition is incompletely understood and may involve both excessive air swallowing and decreased ability to belch. Aerophagia is usually diagnosed on clinical grounds, based on characteristic symptoms in individuals presenting with recognizable excessive air swallowing resulting in increased intestinal gas. Diagnostic criteria for aerophagia have been proposed by the pediatric Rome committees and continued to be refined. Phenotypic variability and symptom overlap with other organic diseases often make the diagnosis and management of aerophagia in children a challenge. Multichannel intraesophageal impedance testing in selected cases may aid in establishing the diagnosis. There is no well-established treatment for childhood aerophagia and in the majority of cases the condition is managed supportively. Education and effective reassurance are often sufficient for the management of the milder cases. In more severe instances, behavioral therapy, psychotherapy, and benzodiazepines may be beneficial.

Epidemiology

The epidemiology of aerophagia is only recently beginning to be unraveled. In the past, this condition was thought to occur mostly in individuals with developmental delay but several recent studies from Sri Lanka have described a fairly high prevalence also in children with normal cognition. In a cross-sectional survey in eight randomly selected schools in four provinces in Sri Lanka, the investigators diagnosed aerophagia using the Rome III criteria in 7.5 % out of 2163 children [1]. The prevalence was higher in older children (peak was in 15-year-olds) and they found no sex difference. Intestinal-related and extraintestinal symptoms were more prevalent among affected children and a higher percentage of affected children were found to be exposed to stressful events when compared with controls. In fewer than one-fifth of the children symptoms were severe enough to interfere with daily activities. In another study, they found that children with aerophagia had abnormal personality traits and hypothesized that this fact may be partly responsible for development and perpetuation of symptoms [2]. Finally, the same authors also reported that behaviors more common in children with aerophagia included being teased, being humiliated, and being treated poorly by others and by parents [3]. A study done in the USA found that aerophagia could be diagnosed in 2.4 % out of 243 African American school-age children visiting a general pediatric clinic for annual school physicals [4]. Among children presenting for an initial evaluation at a gastroenterology clinic and who received a diagnosis of a functional gastrointestinal disorder, aerophagia was found in 1.1 % of children aged 4–9 years and 1.4 % of 10–18 years old [5]. In aggregate, these data suggest that although aerophagia is not as common as other functional disorders such as functional constipation or irritable bowel syndrome, nevertheless it is likely to be encountered fairly frequently in busy pediatric gastroenterology practices. The high prevalence of anxiety and stress in children with aerophagia may explain why treatment with benzodiazepines may be helpful in some cases.

Pathophysiology

With each swallow there is a certain amount of air that enters the stomach [6]. Air is normally present throughout the lumen of the gut from the mouth to the rectum and swallowed air is the prevailing source of gastric gas, because the relative sterile nature of the stomach does not allow gas production from bacterial fermentation. The stomach protects itself from excessive

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distention either through belching (a form of "gas reflux") or by expelling air distally through the pylorus. When air swallowing is excessive, gas fills the gastrointestinal tract, resulting in excessive belching, abdominal distention, flatus, and pain, presumably as a consequence of luminal distention. The mechanism of "excessive" air entry into the intestinal tract is not entirely clear. The swallowing rate for normal adults is approximately 818 (range 524–1064) per 24 h with more frequent swallowing during the day and less at night [7]. Hwang et al. observed by laryngoscopy and fluoroscopy that "pathologic aerophagia" was the result of involuntary paroxysmal cricopharyngeal sphincter openings of the esophagus, like a myoclonus, and that these openings were followed by air swallowing [8]. However, the presence of increased frequency or volume of air swallowing in children with aerophagia has not been convincingly demonstrated yet. Certainly, there is a population of children who swallow excessively, whether volitionally or not, and in so doing increase intragastric and intra-intestinal air resulting in the symptoms of aerophagia. Gum chewing causes an increase in saliva swallowing in both patients with excessive belching and in controls, and leads to an increase in air swallowing in patients with excessive belching 20 min after yogurt ingestion [9].

Some patients with aerophagia have also excessive belching. Belching occurs through the same mechanism as gastroesophageal reflux, namely a transient lower esophageal sphincter relaxation. When excessive air is ingested, there is distention of the gastric fundus, a known trigger for the relaxation of the lower esophageal sphincter, causing increased frequency of air expulsion [10, 11]. In some patients, the belching may not represent expelled intragastric air, but rather elimination of air that accumulates in the esophagus above the stomach ("supragastric belching") [12, 13]. The latter group of patients, who presents with symptoms limited to frequent eructation, does not truly belong to the category of aerophagia even though they present with a similar phenotype [14].

Finally, there is a subgroup of children who seem unable to belch and in those patients symptoms of aerophagia may actually be related to inability to expel even a physiologic amount of swallowed air. This is a clinical scenario akin to patients who develop symptoms of "gas bloat" after a fundoplication has impaired their ability to belch and/or vomit [15].

Diagnosis

There is no single diagnostic test that can be used to conclusively diagnose aerophagia. The diagnosis may be easy in the presence of the typical signs and symptoms of air swallowing which may be visible and often audible, accompanied by excessive belching and flatus. The abdomen is typically flat in the morning and becomes progressively more distended throughout the day. The abdominal distension then improves during the night by absorption of gas and by passage of flatus. In infants, there may be a history of nursing from an empty bottle, or prolonged sucking on a pacifier. In older children, large amounts of air can be swallowed drinking excessive amounts of carbonated beverages. The Rome IV Child-Adolescent Committee established symptoms-based diagnostic criteria for aerophagia in children [16] (Table 40.1).

The differential diagnosis of aerophagia is fairly broad and involves other entities which present with abdominal distension. When excessive air swallowing is either not recognized by the medical provider or denied by the parents, the child may be suspected of having gastroparesis or other more generalized motility disorders, such as chronic intestinal pseudo-obstruction. These are conditions which may also present with increasing amount of abdominal distension throughout the day. Bacterial overgrowth, malabsorption (particularly celiac disease and mucosal disaccharidases deficiency), tracheoesophageal fistula, and constipation are other fairly common etiologies of abdominal distension and excessive flatus in children. As patients with aerophagia are usually otherwise healthy with normal growth and development, extensive testing to rule out several other diseases is rarely necessary.

When radiological studies are obtained (Fig. 40.1a, b), there is usually evidence of a dilated stomach and small bowel full of air in the absence of other signs of bowel obstruction. The excessive amount of intraluminal gas is especially obvious when the studies are obtained in the evening, at the apex of the abdominal distension. The esophageal "air sign," defined as an abnormal air shadow on the proximal esophagus adjacent to the trachea on a full-inflated chest radiograph, has been reported in the majority of children with aerophagia in one study [17] but its specificity for this condition has not been evaluated. Multichannel intraesophageal impedance is able to differentiate air from wet swallows (Fig. 40.2) because air conducts current poorly and thus it has a high impedance, leading to a dramatic increase in baseline. Impedance can be used to diagnose aerophagia by detecting an increased frequency of air swallows and may also be used to diagnose supragastric belching in children [18].

Table 40.1 Rome IV diagnostic criteria for aerophagia

Diagnostic criteria[a] must include all of the following:
1. Excessive air swallowing
2. Abdominal distention due to intraluminal air which increases during the day
3. Repetitive belching and/or increased flatus
4. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition

[a]Criteria fulfilled for at least 2 months prior to diagnosis

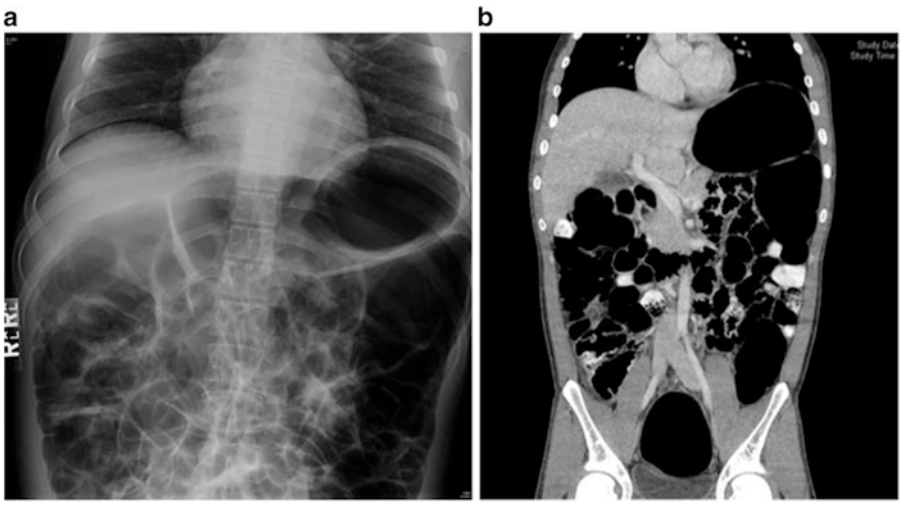

Fig. 40.1 Plain radiograph (**a**) and computerized axial tomography (**b**) of the abdomen showing gaseous distension of the stomach, small and large bowel in two children with aerophagia

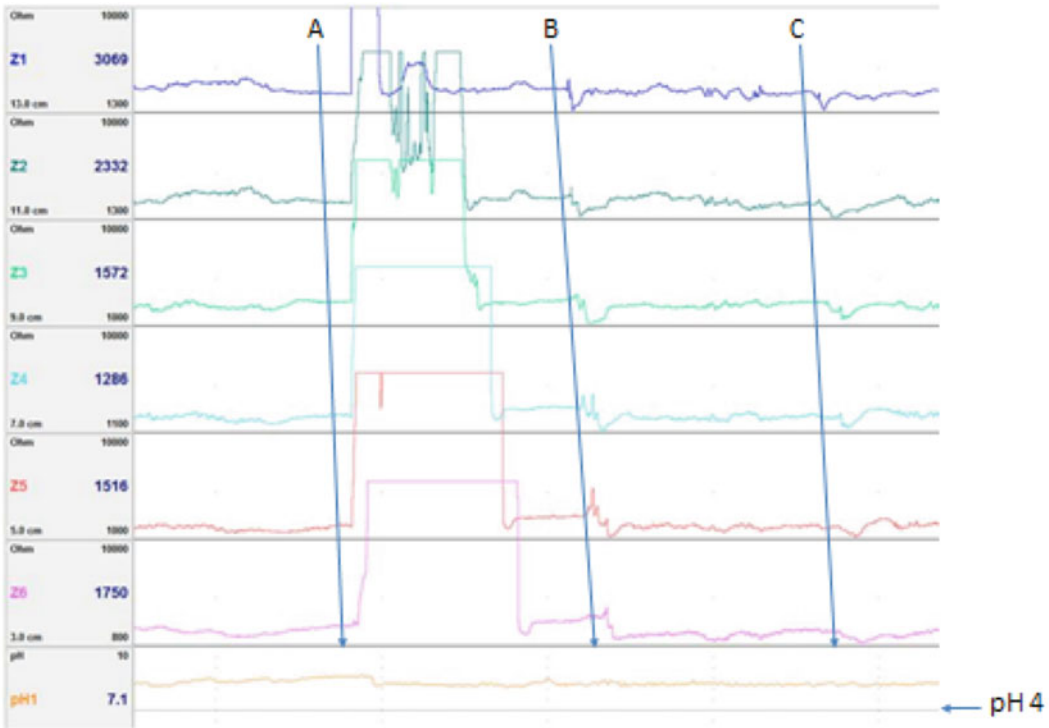

Fig. 40.2 The figure depicts three different types of swallows: (**a**) air swallow, (**b**) mixed swallow, (**c**) wet swallow

Treatment

Management of aerophagia needs to be tailored based on the severity of symptoms generated. Although generally felt to be a benign condition, aerophagia has been associated with development of colonic volvulus [19] and colonic perforation [20]. Most commonly, children with aerophagia are brought to the attention of care providers with complaints of noisy swallow, excessive belching, or abdominal distention. Once a diagnosis of aerophagia has been made, education about what generates the symptoms and effective reassurance that no serious underlying disease is present are the most often employed measures and may represent the most effective intervention [21]. Understanding the mechanisms underlying the excessive air swallows may be very reassuring for the parents and the child. Elimination of gum chewing and carbonated beverages and avoidance of drinking from a straw can be helpful. When the air swallowing is visible and/or audible during the clinic visit,

the clinician can help the child and the caretakers become aware of air swallows so that the behavior is minimized. Keeping the mouth wide open after completion of a meal may minimize air swallow, as it is impossible to swallow with an open mouth. When patients with excessive belching are unaware that they are being observed or when they are distracted, the incidence of belching is significantly reduced [22]. These findings underline the importance of psychological factors and provide rationale for behavioral therapy. Hypnosis has been suggested as a mode of therapy in a case report [23]. When primary psychological disorders, especially an anxiety disorder, are present, they should be treated [24]. Different behavioral and mechanical techniques, incorporating biofeedback, have been tried, though only in small trials and rarely with children, to promote self-awareness of swallowing and limit its frequency [25, 26]. Pharmacologic therapy has a limited role in the treatment of children with aerophagia due to the lack of thorough understanding of the pathophysiology of this condition and the potential side effects of the medications that have been tried. Benzodiazepines have been employed on the basis that the emotional state may impact swallowing rates and due to their efficacy in the treatment of myoclonus. There have been two reports in which clonazepam was shown to be effective in children with aerophagia with and without mental retardation [8, 27]. Baclofen is a muscle relaxant used to treat spasticity and movement disorders. It has been shown to improve symptoms of rumination and supragastric belching [28] and may have a role in the treatment of aerophagia. In the most severe cases, nasogastric decompression, a venting gastrostomy or even an esophagogastric separation and abdominal esophagostomy via jejunal interposition may be justified [29].

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Rumination Syndrome

41

Anthony Alioto and Carlo Di Lorenzo

Rumination syndrome has been reported in the past as being typical of emotionally deprived and often cognitively impaired infants and adults. More recently, there have been large case series describing it as occurring in older children and adults with intact cognitive abilities. Given the substantial differences in etiologic factors, phenotypic presentation, and treatment strategies between infantile and adolescent forms, this chapter will focus solely on rumination syndrome in older children and adolescents.

Despite a recent increase in scientific publications on the subject, rumination syndrome remains poorly understood and infrequently recognized, even by practitioners with a great deal of clinical experience. Its presentation is so characteristic that the high frequency of misdiagnoses is perplexing and likely related to the unfortunate convergence of several factors. First and foremost, there may be some degree of discomfort in making a diagnosis of a disorder that has a behavioral component. In this regard, rumination may be similar to functional dyspepsia or irritable bowel syndrome. In these conditions, physicians may feel more comfortable with a "medical" diagnosis such as gastritis, gastroesophageal reflux disease (GERD), or colitis rather than embarking in a lengthy and at times antagonistic discussion with the family of what constitutes a functional disorder.

Second, there is no easy "test" to conclusively diagnose rumination syndrome. In Western culture, medicine (and patient expectations) often is based on the biomedical model which postulates that a symptom is due to a demonstrable anatomical, inflammatory, serologic, immune, or other system dysregulation. Without a laboratory, radiological, or endoscopic test demonstrating a pathognomonic abnormality, many practitioners and patients feel uncomfortable with the diagnosis. The more sophisticated diagnostic tests which *could* be used to diagnose rumination are not widely available.

Third, the lack of a standard and relatively easy to implement therapy for this condition may give some providers a sense of futility when making such a diagnosis for which they have little therapeutic advise to offer. In order to guide the practitioner, we will discuss the most recent understanding of the epidemiology, pathophysiology, diagnosis, and therapy of rumination syndrome.

Epidemiology

Traditionally, this condition has been considered as having a low prevalence and being more common in girls [1]. As described earlier, the insufficient recognition of rumination syndrome as a diagnostic entity undermines efforts to understand its prevalence. Further complicating estimates, the symptoms of rumination syndrome overlap with symptoms of more readily recognized conditions such as motility disorders or eating disorders [2–6]. A recent school study in Sri Lanka used a self-administered questionnaire given to 2163 children between the age of 10 and 16 years and found symptoms consistent with rumination syndrome in 5 % of individuals, with equal prevalence between boys and girls [7]. It is unclear how many of these children had true rumination syndrome versus GERD, a much more common condition at this age.

Patients with rumination syndrome often are evaluated by numerous physicians over the course of several years prior to receiving the correct diagnosis [3, 8]. In the interim, they undergo multiple medical evaluations and diagnostic tests, which are distressing, costly, and may uncover incidental findings which then make the final diagnosis of rumination syndrome even more difficult to accept. In one sample of adolescents [3], onset of rumination symptoms occurred around age 13 years, with the diagnosis of rumination syndrome ultimately given approximately 2 years later.

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Physical or psychological stressors often occur just before the onset of the symptoms in a sizable subset of subjects, and a substantial portion of diagnosed patients have associated physical illnesses or concomitant psychological disorders [3, 8].

Pathophysiology

The precise etiology of rumination syndrome remains unknown at this time. Even so, many patients' histories are suggestive of a trigger at the onset of symptoms, such as an infectious or inflammatory gastrointestinal disease or stressors involving emotional arousal. After the initial stressor has resolved, the vomiting behavior appears to remain in place, almost similar to a motor tic.

Gastric motor and sensory abnormalities have been reported in rumination syndrome. Barostat and manometric studies have demonstrated gastric hypersensitivity with more frequent episodes of lower esophageal sphincter relaxation in response to gastric distension. Some individuals have impaired postprandial gastric accommodation [9]. A mild degree of gastroparesis may be found in approximately 40 % of adolescents with rumination [3], although emptying studies are difficult to interpret in individuals who continuously regurgitate during the test. A poorly accommodating fundus and an impaired antral pump may lead to postprandial distress that is relieved by expulsion of the food just ingested. As such, the behavior of regurgitating gastric contents serves to relieve epigastric discomfort and becomes a conditioned response to the ingestion of food or fluid.

Upon ingestion of food (or even in anticipation of ingestion of food), a sequence of behaviors has been generated, including contraction of the abdominal wall, opening of the lower and upper esophageal sphincter, and subsequent expulsion of food [10]. Recently, three different mechanisms of rumination were described in adults: (1) primary rumination, in which the abdominal pressure increase occurs before the retrograde flow, (2) secondary rumination, in which there is an increase in abdominal pressure following the onset of a reflux event, and (3) supragastric belch-associated rumination, consisting of a supragastric belch, often associated with air swallowing, immediately followed by a rumination event [11]. It is unclear yet whether these different mechanisms may direct different treatment strategies or if they are associated with different prognosis.

Clinical Features

The main clinical characteristic of rumination is the timing of the act of vomiting. There are very few other medical gastrointestinal diseases associated with vomiting within seconds or minutes from food ingestion. Although the regurgitated gastric contents may be re-swallowed, in adolescents they frequently are expelled. Rumination persists up to an hour after eating and does not occur at night [12]. Table 41.1 shows some of the features differentiating rumination from other clinical entities. Weight loss is a common feature of the most severe forms of rumination syndrome and may lead to the need for tube feedings or even parenteral nutrition. Other symptoms, particularly abdominal pain, heartburn, and nausea, are less frequently reported, but often act as a "signal," allowing patients to recognize when rumination is about to occur.

Diagnosis

Rumination syndrome is a clinical diagnosis [6] and very minimal testing should be needed in the classic cases. A patient who satisfies the symptoms-based Rome criteria for this condition (Table 41.2) should need no further investigation. Pointing out to the patients and to the parents how saliva is easily swallowed but even a sip of water causes symptoms is particularly enlightening with regard to the behavioral component of this disorder.

Antroduodenal manometry is not always necessary to make the diagnosis, but it can be considered as the "big convincer" in cases when the families or the patients are not yet confident of the diagnosis of rumination syndrome. Manometry may also be used to rule out the presence of an underlying motility disorder, a common fear among families of patients with this disorder. In patients with rumination syndrome, antroduodenal manometry shows essentially normal fasting and postprandial motor patterns [6, 13]. The characteristic manometric abnormality is a

Table 41.1 Differential diagnosis of rumination syndrome from other conditions presenting with emesis in adolescents

	Vomiting	Esophagitis	Prokinetics	Fundoplication
Rumination	During or minutes after meal	No	Not helpful	Not helpful
Achalasia	Hours after meal	Often (from stasis)	Not helpful	Contraindicated
GERD	After large meals or when lying down	Often	Helpful	Helpful
Gastroparesis	Hours after meal	No	Helpful	Not helpful
Cyclic vomiting	Intermittent, unrelated to meal	During episodes	Not helpful	Not helpful

Table 41.2 Rome IV criteria for adolescent rumination syndrome

Diagnostic criteria[a] Must include all of the following
1. Repeated regurgitation and rechewing or expulsion of food that:
(a) Begins soon after ingestion of a meal
(b) Does not occur during sleep
2. Not preceded by retching
3. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition. An eating disorder must be ruled out

[a]Criteria fulfilled for at least 2 months prior to diagnosis
For more information, see Benninga et al.: http://www.ncbi.nlm.nih.gov/pubmed/27144631 Or Hyams et al.: http://www.ncbi.nlm.nih.gov/pubmed/27144632

synchronous increase in pressure ("r" waves) across both gastric and duodenal recording sites when the rumination occurs. The "r waves" are thought to represent the effect of an increase in intragastric or intra-abdominal pressure generated by the contraction of the skeletal abdominal muscles. Interestingly, under the pressure of being in a laboratory setting with constant attention being paid to their symptoms, some adolescents with rumination are able to eat the test meal during the manometry study with minimal or no symptoms (Fig. 41.1).

Impedance-manometry monitoring allows distinction between rumination from GERD and supragastric belching. During rumination, esophageal liquid retrograde flow is driven by an early rise in intragastric pressure preceding the peak pressure observed during straining [14]. It has been suggested that the diagnosis of rumination syndrome can be made when reflux events extending to the proximal esophagus are associated with an abdominal pressure increase >30 mm, because such increase is usually not seen in patients with GERD. The impedance study will also confirm the characteristic absence of nighttime reflux events in patients with rumination syndrome.

Treatment

As practitioners and researchers strive to understand the pathogenesis of this complex functional disorder, many have proposed mechanisms by which rumination occurs and is maintained. Interestingly, while not formally referring to rumination as a habit disorder, most authors discuss rumination occurrence and treatment very much like that of a habit disorder [10, 15–18]. Therefore, this chapter conceptualizes rumination syndrome in these terms, and the components of treatment described in the literature for rumination syndrome are presented and organized as such.

Education and Reassurance

Several authors have discussed how accurate diagnosis and reassurance often provide considerable relief to families and patients [1, 11, 19]. Education about rumination syndrome may allow for a reduction in anxiety, as patients are provided with a diagnosis and understand that no structural or intrinsic motility problems exist. In addition, accurate description of the disorder may allow patients to be a more active part in their own treatment.

Presentation of rumination syndrome from a biopsychosocial perspective allows families to understand the interplay among physical, behavioral, emotional, and situational factors [15]. The educational intervention should include a discussion of why no further testing is needed, how rumination syndrome can be diagnosed by symptoms (and it is not simply a diagnosis of exclusion), and that the condition is treatable using behavioral interventions. In our experience, families who continue to seek further diagnostic testing and a "medical" explanation for the rumination tend to be less invested and less successful with treatment.

Many patients who have not heard of rumination syndrome often interpret their vomiting as their stomach not being able to "handle" food or fluid, and therefore "rejecting" the food, contracting, and forcing the food upward. An important aspect of the educational process is describing the pathophysiology of rumination with a focus on contraction of the intercostal muscles and abdominal wall as the driving force behind the expulsion of stomach contents [20]. Triggers for the behavior are discussed, including food or fluid intake, the rise of dyspeptic symptoms, or even the anticipation of eating or drinking. Finally, the role of autonomic nervous system arousal (via worry, nervousness, and anxiety) in rumination is discussed with the patient and family.

Behavioral Observation

The importance of observing the patient eat or drink and then ruminate cannot be overemphasized. As described earlier, different mechanisms may underlie the patient's rumination [11]. In our experience, no two patients with a diagnosis of rumination have been exactly the same with regard to the antecedent sensory experience, the types or amounts of food or fluid that trigger rumination, or the manner in which they manage the rumination (e.g., reswallow, expel). Observation of the rumination allows for both further evaluation of the patient and the ability to increase the patient's awareness of the behavior.

Awareness Training

In order to increase patient awareness of rumination and its antecedents (as discussed in the educational portion of treatment), patients in our program typically take part in two observation mealtimes. During the first meal, patients are requested to eat a meal at their typical pace, and to ruminate and vomit as they normally would outside of the medical

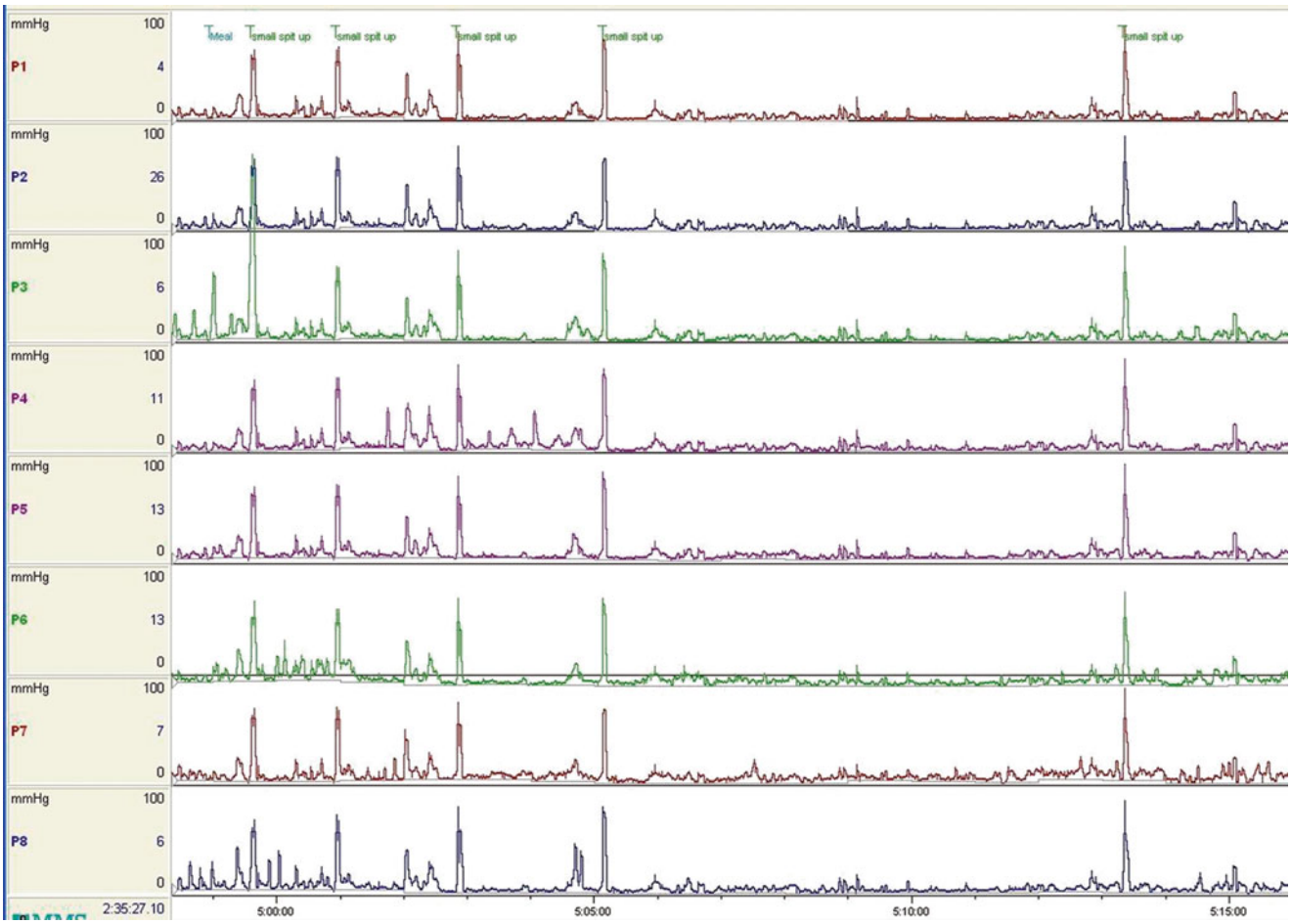

Fig. 41.1 An example of an antroduodenal tracing from an adolescent with rumination syndrome. The end of the meal is marked and almost immediately afterwards, the patient begins to have episodes of "small spit up," marked as such on the tracing. Those events are associated with a simultaneous increase in pressure in all recording sites (known as "r waves")

setting. The clinician requests that the patient attend to the abdominal wall contractions as they occur. Information gathered includes how often the patient ruminates during this natural meal (or if rumination does not commence until the mealtime ends), the pace of the patient's eating, the patient's posture, how they attempt to manage rumination, and observable symptoms such as belching.

At the second observation meal, the clinician directs the patient as to how much to eat or drink at 5-min intervals. For example, the clinician may request that the patient drink one ounce of juice, or take one bite of mashed potatoes. During this second meal, the clinician continuously records data such as the amount of food or fluid ingested at each interval, the number of times the patient ruminates or vomits, and requests that the patient rate their most common dyspeptic symptoms on a scale of 0–10 every 5 min. By the end of the meal, a picture often emerges of a gradual increase in dyspeptic symptoms, a gradual increase in rumination, and resolution of the dyspepsia with emesis. This information is shared with the patient, as they recognize the relationship between their dyspeptic symptoms and rumination behavior. These observation mealtimes also allow the clinician to obtain a "starting point" for treatment, recognizing the amount of food that can trigger rumination and how soon into a mealtime the rumination commences.

Awareness training continues during treatment mealtimes (typically 3 times each day, lasting around 20–30 min). Using the data from the observation meals as a starting point, the clinician designs mealtimes with the patient tracking rumination frequency, vomiting, and the intensity of dyspeptic symptoms at 5-min intervals. While it is relatively uncommon for the rumination behavior or dyspeptic symptoms to change significantly over the first few days, the data provides a solid baseline for the clinician, and increased awareness on the part of the patient and parent [21].

The use of biofeedback has been described by several authors as a beneficial intervention in patients with rumination syndrome [3, 16, 22, 23], at times with minimal descrip-

tion of the specific biofeedback modality employed or the proposed mechanism by which the biofeedback is thought to have allowed for improvement. To further increase awareness of the physical response to rumination, our program has utilized biofeedback in multiple ways. First, many patients benefit from the use of surface electromyography (sEMG) monitoring the abdominal muscles to further elucidate the muscle contractions that occur during episodes of rumination [20, 24]. Second, when instructing on the use of diaphragmatic breathing, the use of respiration belt or sensor with biofeedback often is particularly beneficial in increasing awareness of and adjusting aspects of respiration such as breathing rate, patterns (e.g., breath holding), and depth of respiration.

Third, heart rate variability (HRV) biofeedback can be beneficial in providing the patient with continuous feedback about their stress response/relaxation response during and after mealtimes. Functional gastrointestinal disorders recently have been understood in terms of the multiple pathways that influence symptom presentation, with autonomic nervous system dysregulation playing a role [25, 26]. The autonomic nervous system's reactivity and recovery has an impact on symptom presentation in patients with functional gastrointestinal disorders such as irritable bowel syndrome [27]. It also has been demonstrated that biofeedback approaches (i.e., instruction on autonomic nervous system regulation) allow for increased vagal tone as well as symptom improvement in patients with functional abdominal pain [28]. Given the role of autonomic dysregulation in functional disorders, it is likely that similar mechanisms contribute to the challenges demonstrated by patients with rumination syndrome.

Environmental or Internal Factors

The clinician should be aware of environmental factors that may influence the patient's rumination behavior. While rumination typically is associated with the ingestion of food, there are some patients who begin to ruminate when food is merely present, or when food first touches the tongue. Another common environmental factor to be aware of is the presence of the patient's emesis container (e.g., a bag, cup, or other vessel into which patients vomit throughout the day). Removal of the container typically allows for improved focus and awareness of rumination on the patient's part, and greater motivation to control vomiting.

Internally, patients typically have the expectation that everything they eat or drink will be ruminated and or vomited. As such, they inadvertently engage in self-talk that likely serves to diminish motivation and potentially heighten the stress response during mealtimes. Such automatic thoughts (e.g., "This is going to hurt" or "I'm going to throw this up eventually") often are seen in patients with comorbid anxiety or depressive symptoms.

The Premonitory Urge

Another internal cue for rumination is the patient's sensory experience after ingestion of food or drink. Patients with rumination often describe a sense of nausea, pain, burning, pressure, bloating, or early satiety that increases with time and increased intake [8, 20, 29]. Similar to the experience of patients with more traditional motor tic or habit disorders, the dyspeptic symptoms may serve as a premonitory urge for the motor behavior to occur, in this case, abdominal wall contraction.

Several approaches can be undertaken to reduce the premonitory urge, which may reduce rumination. Pharmacological approaches may allow for a reduction in pain, bloating, burning, or nausea associated with eating. In addition, many patients benefit from interventions that allow for a shift in their attention away from the discomfort. One such strategy we have found beneficial is reading children's books aloud during the mealtime. In addition to providing a distraction, reading aloud also encourages patients to adapt their breathing pattern into more of a diaphragmatic breath with slow exhalation. Patients are taught to recognize the relationship between the sensory and behavioral aspects of rumination and to utilize self-regulatory and competing responses either at the detection of the premonitory urge or at various points during a mealtime [10, 18, 20].

Competing Response

Diaphragmatic breathing has been described as a mainstay in the treatment of rumination syndrome [10, 11], with authors suggesting that diaphragmatic breathing serves as a competing response to rumination [17, 18, 29]. The physical act of rumination involves a simultaneous contraction of the intercostal and upper abdominal muscles, and relaxation of the lower esophageal sphincter [20, 30]. This behavior places considerable pressure on the abdominal cavity, thereby resulting in intragastric pressure forcing gastric contents upward. As such, the focus of behavioral therapy has focused on having the patient utilize strategies to mitigate the impact of these contractions on the abdominal wall. Recently, Barba and colleagues [20] utilized a biofeedback-focused approach to instruct patients to increase their awareness of the use of these muscles and thereby correct and reduce the contractions. With regard to the behavior, the authors found that patients (adolescents and adults) were able to modify the behavior, decrease the number of rumination events during a meal, and maintain the gains up to 6 months later.

Supplemental Feeding and Gradual Refeeding

Patients with more severe rumination syndrome typically report significant weight loss and even hospitalizations due to

malnutrition and dehydration [31]. Prior to formal treatment for rumination, stabilization of nutrition and weight is strongly encouraged. Special means of alimentation with post-pyloric feedings, either through naso-jejunal or gastro-jejunal feeding catheters, may be used initially to maintain adequate nutritional status when weight loss is significant and should always be attempted prior to parenteral nutrition.

Authors have discussed the importance of having patients slowly reintroduce food and fluid intake [32]. Gradual reintroduction of oral intake allows patients to practice and utilize their self-management skills while working with increasingly challenging quantities of food and tolerating the discomfort that arises with gastric distension. The use of frequent, small feeding trials seems to provide additional benefits to patients, including repeated reexposure to a stressful stimulus (i.e., actual eating/drinking and/or anticipatory anxiety about eating/drinking). This measured approach provides patients with a sense of self-efficacy as they make progress and have successful experiences with keeping food down. As patients progress in their ability to not expel food, enteral feedings can be reduced proportionally [31].

In our work with patients with rumination syndrome, we emphasize the importance of reswallowing any gastric contents that are propelled to the mouth. Prior to treatment, many patients experience relief from their dyspeptic symptoms upon vomiting. Our experience with reswallowing is that it allows the patient to practice the self-regulation skills while also not allowing the act of rumination and subsequent vomiting to be negatively reinforced.

Pharmacological Interventions

To date, drug treatment in children with classic rumination syndrome has proven to be minimally beneficial. Baclofen is an agonist of the γ-aminobutyric acid B receptor, which decreases transient lower esophageal sphincter relaxations, increases sphincter pressure, and decreases swallowing rate. Baclofen has been shown to decrease retrograde flow events, regurgitation, and belching in adult patients with rumination or supragastric belching [33]. During the behavioral treatment for rumination, medications may be used to facilitate sleep, address psychiatric comorbidities, treat other somatic symptoms (e.g., headaches, nausea, early satiety), and to aggressively deal with constipation, as stool retention has been shown to trigger dyspeptic symptoms [34].

Comorbid Psychological Factors

A subset of patients with rumination syndrome also has comorbid emotional difficulties including depression, anxiety, histories of abuse, and life stressors [3, 8, 35]. The relationship between emotional state, autonomic nervous system activation, and the experience of pain has been widely recognized [24, 36, 37]. While these comorbid conditions likely are not the cause of the rumination, failure to identify and address these challenges may have a deleterious impact on treatment [8]. Patients with comorbid emotional difficulties may experience greater discomfort during treatment, anticipatory anxiety, and experience greater emotional distress as a result of the discomfort.

Interdisciplinary Approaches

As discussed earlier, patients with rumination syndrome tend to be a heterogeneous group in terms of many factors including their triggers, comorbid medical and psychological challenges, and severity of their rumination. As such, a one-size-fits-all approach to treatment is not warranted. It may be the case that patients with fewer comorbid difficulties and less severe rumination may benefit from less complex interventions (e.g., one or several sessions of diaphragmatic breathing). More complicated patients may fare better in a multidisciplinary or interdisciplinary setting.

Several authors have discussed programmatic approaches to the treatment of rumination syndrome [3, 16, 24]. Intensive treatment approaches allow multiple disciplines to address similar components of the patients' challenges in a complementary manner, while providing a more controlled environment in which treatment may take place. Treatment in an inpatient medical setting provides the additional benefit of close monitoring of associated medical difficulties (e.g., severe nausea, pain, transition from enteral feedings).

Evaluating Progress

Several methods of assessing treatment progress have been utilized throughout the literature. Perhaps the most common method of measurement has been monitoring of the rumination frequency throughout the day [17, 20, 32]. Others have examined outcome variables such as global improvement [3], the duration of rumination episodes [38], and rumination intensity [39].

Other aspects of the syndrome should be assessed as well, including changes in the patient's experience of sensory triggers [20], or improvements in caloric intake and retention throughout the day [8, 16]. By examining these individual aspects of the rumination syndrome, authors have elucidated many important variables of interest. Unfortunately, such diversity in measurement makes comparison of treatment approaches across studies problematic and suggests that development of a measure of syndrome severity and more standardized outcome measures is imperative.

Conclusion

Rumination syndrome is a relatively easily diagnosed, but often misidentified condition that has a significant impact on patients' quality of life. Rumination has been shown to be responsive to behavioral interventions. While some cases may benefit from a simplified treatment protocol carried out as an outpatient [6], more disabled patients may benefit more from an intensive, programmatic approach. Families who accept the diagnosis, have a solid understanding of the mechanisms that maintain rumination, and provide the patient with ongoing support tend to demonstrate better recovery. Further research will serve to clarify patient and family variables that may be empirically predictive of treatment success [27].

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Functional Constipation in Children

42

Ilan J.N. Koppen and Marc A. Benninga

Constipation is a common and bothersome problem in children. It may present with infrequent bowel movements with fecal incontinence, hard stools, large stools, painful defecation, and abdominal pain [1]. In approximately 95 % of children with constipation, no organic cause can be identified, these children suffer from functional constipation (FC) [2]. The prevalence of FC ranges between 0.7 and 29.6 % and it occurs more often in girls than in boys (ratio: 2.1:1) [3]. The diagnosis of FC is based on the pediatric diagnostic Rome criteria for functional gastrointestinal disorders (Table 42.1) [4]. These criteria were revised in the spring of 2016 [5, 6] (for more information, see Benninga et al.: http://www.ncbi.nlm.nih.gov/pubmed/27144631 or Hyams et al.: http://www.ncbi.nlm.nih.gov/pubmed/27144632.

Physiology

Meconium Passage and Defecation Frequency

In more than 99 % of healthy term neonates, the first meconium passes within the first 48 h of life [5, 6]. Delayed passage of the first meconium beyond the first 48 h of life is suggestive for an organic defecation disorder (e.g., Hirschsprung's disease). During the first months of life, the defecation frequency may vary from child to child, this is partially dependent on feeding type; breastfed children have a higher defecation frequency than formula-fed infants [6]. In the first weeks of life, the defecation frequency lies around 4 stools a day, this frequency gradually decreases over time until it is approximately once a day in children at the age of 4 years [6, 7]. In older children, defecation usually occurs either daily or every other day [8].

Defecation Dynamics

The physiological dynamics of defecation are complex and rely on several intricate processes involving the autonomic and somatic nervous system, the pelvic floor muscles, and the internal and external anal sphincters. In the colon, feces is propelled by propagating colonic contractions. Several different colonic motor patterns have been described [9, 10], but the most well-recognized propagating motor patterns are high-amplitude propagating contractions (HAPCs). These motor patterns are associated with the mass movement of colonic content and spontaneous defecation in healthy adults [11, 12]. Anterograde propagation of feces through the colon leads to filling of the rectum, which induces a relaxation of the internal anal sphincter, allowing feces to travel further down the anal canal; this reflex is known as the recto-anal inhibitory reflex (RAIR). Subsequently, sensory stimuli caused by rectal distension and by the contact between fecal material and the mucosa of the proximal part of the anal canal result in an urge to defecate. At this point, voluntary contraction of the external anal sphincter can postpone defecation, by moving the fecal load back, higher up in the anal canal and rectum, until the place and time are appropriate for defection. When defecation is initiated, voluntary relaxation of the external anal sphincter and the pelvic floor musculature (i.e., the puborectalis muscle and levator ani) allows for an easy defecation process. In young children, this can be promoted by proper support of the feet when sitting on the toilet and a relaxed posture. Then, by gently increasing the intra-abdominal pressure, stools can be expelled from the rectum.

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Table 42.1 ROME III and Rome IV criteria for functional constipation

Age	<4 years	Developmental age of ≥4 years
Rome III criteria	• <3 defecations per week	• <3 defecations in the toilet per week
	• ≥1 episode of fecal incontinence per week after the acquisition of toileting skills	• ≥1 episode of fecal incontinence per week
	• History of excessive stool retention	• History of retentive posturing or excessive volitional stool retention
	• History of painful or hard bowel movements	• History of painful or hard bowel movements
	• Presence of a large fecal mass in the rectum	• Presence of a large fecal mass in the rectum
	• History of large diameter stools which may obstruct the toilet	• History of large diameter stools which may obstruct the toilet
	Must fulfill ≥2 criteria for ≥1 month prior to diagnosis	Must fulfill ≥2 criteria at least once per week for ≥2 months prior to diagnosis
		Insufficient criteria for diagnosis of IBS
Rome IV criteria	Must include 1 month of at least 2 of the following in infants up to 4 years of age:	Must include 2 or more of the following occurring at least once per week for a minimum of 1 month with insufficient criteria for a diagnosis of irritable bowel syndrome:
	1. 2 or fewer defecations per week	1. 2 or fewer defecations in the toilet per week in a child of a developmental age of at least 4 years
	2. History of excessive stool retention	2. At least 1 episode of fecal incontinence per week
	3. History of painful or hard bowel movements	3. History of retentive posturing or excessive volitional stool retention
	4. History of large-diameter stools	4. History of painful or hard bowel movements
	5. Presence of a large fecal mass in the rectum	5. Presence of a large fecal mass in the rectum
	In toilet-trained children, the following additional criteria may be used:	6. History of large diameter stools that can obstruct the toilet
	6. At least 1 episode/week of incontinence after the acquisition of toileting skills	After appropriate evaluation, the symptoms cannot be fully explained by another medical condition
	7. History of large-diameter stools that may obstruct the toilet	

ROME III [4] and Rome IV (Benninga et al.: http://www.ncbi.nlm.nih.gov/pubmed/27144631 or Hyams et al.: http://www.ncbi.nlm.nih.gov/pubmed/27144632)

Pathophysiology

The pathophysiology of FC is incompletely understood; multiple factors are likely to play a role in its pathogenesis and may affect different phases of the physiological defecation dynamics.

Age of Manifestation

FC occurs in children of all ages, but there are three phases in life when children seem to be more prone to develop constipation: (1) in infancy, concomitant with changes in feeding (e.g., change from breastfeeding to formula-feeding, introduction of solid foods); (2) around the time of toilet training; and (3) in school children who avoid going to the toilet at other places than home [13]. This suggests that both dietary and behavioral factors play an important role in the pathogenesis of FC.

Stool Withholding Behavior

One important recognized etiologic factor, especially in young children, is stool withholding behavior. This often occurs after a negative experience such as a hard, painful, or frightening bowel movement [14]. Stool withholding behavior can lead to the accumulation of a large fecal mass in the rectum that is difficult to evacuate, also known as fecal impaction. Fecal impaction may lead to overflow fecal incontinence which is the involuntary loss of soft stools that pass the solid, obstructing, fecal mass. Stool withholding can lead to a negative chain of events; due to a painful defecation experience, the child voluntarily retains the stools in an attempt to prevent another painful bowel movement, causing the stools to become harder and more difficult to evacuate, leading to more pain during defecation. Withholding behavior may eventually lead to dyssynergia, this occurs when the coordination of the muscles involved in defecation are inadequately coordinated during defecation. Instead of relaxing the muscles involved in normal defecation, muscles are tightened in a poorly

coordinated attempt at defecation, preventing stools to be expelled from the rectum and sustaining constipation.

Colonic Dysmotility

Propagation of feces through the colon is an essential step in the physiology of defecation. In children with long-standing symptoms of FC the passage of feces through the colon is often delayed [15]. It is not entirely clear whether this delay in colonic transit time plays a causative role or if it is an effect of long-standing constipation and becomes a perpetuating factor, resulting in a detrimental causal sequence.

Studies utilizing colonic manometry have revealed that in children with intractable FC, several types of colonic dysmotility can be differentiated. In healthy humans, stretching of the stomach after a meal induces an increase in motility of the colon, this response is known as the gastrocolic reflex. Colonic manometry studies have shown that this reflex is impaired in a subset of children with FC, which may indicate an impaired extrinsic innervation [16, 17]. Furthermore, it has been shown that a proportion of children with FC have incompletely propagating HAPCs or a general lack of HAPCs in response to a stimulant laxative, which likely implies an intrinsic (neurogenic or myogenic) pathophysiological process. Once again, it remains uncertain whether these findings are cause, effect, or a combination of both.

Psychosocial Factors

Although the precise underlying pathophysiological mechanisms are not always clear, psychosocial factors such as major life events, socioeconomic status, educational level, and parental child-rearing attitudes might play a role in the pathophysiology of FC [3, 18, 19]. Furthermore, behavioral disorders such as autism spectrum disorders and attention deficit hyperactivity disorder are associated with a higher risk of childhood constipation [20, 21].

Genetics

Since FC seems to occur more often in certain families, genetic factors may contribute to the etiology of childhood constipation [22]. However, studies have failed to identify mutations in specific genes associated with FC [23].

Microbiota

Gut microbiota differences have been identified between children with and without FC, suggesting that gut microbiota may play a role in the pathogenesis of FC [24]. One of the possible mechanisms in which the gut microbiota may potentially influence gut motility is by the production of methane as a consequence of anaerobic fermentation of carbohydrates and the production of hydrogen in the gut [25]. There is strong evidence from animal studies that methane delays intestinal transit, possibly acting as a neuromuscular transmitter, and methane production has been associated with constipation in adults [25–27].

Bile Salts

There has been an increasing interest in bile salt metabolism as a potential pathophysiological factor in FC; deconjugated bile salts have the potential to function as endogenous laxatives by increasing colonic motility and fluid secretion [28, 29]. In a subset of children with FC, bile acid metabolism has been shown to be altered, leading to a decreased secretory activity. This suggests that bile acid metabolism may play a role in the pathophysiology of constipation in a subset of children [30].

Evaluation

The evaluation of a child with constipation should always aim to differentiate between FC and constipation due to an organic cause. The diagnosis of FC is based on a thorough medical history and a complete physical examination, additional investigations are usually not required [2].

Medical History

In the medical history, questions should address defecation frequency, stool consistency, painful bowel movements, size of the stools, episodes of fecal incontinence, and a history of withholding behavior (Table 42.1). Keeping a daily bowel diary can be useful to gather reliable information about a child's bowel habits. The Bristol Stool Scale or the Modified Bristol Stool Form Scale for Children can be helpful in the assessment of stool consistency [31]. Special attention should be paid to questions about withholding behavior, as this behavior may not be recognized as such by parents and may even be wrongfully interpreted as straining to defecate. Questions regarding stool withholding behavior should therefore be clear and illustrated with examples. In infants, withholding may be characterized by grunting, arching of the back, and tightening of the legs. In toddlers, squeezing the buttocks together, crossing the legs, standing on the toes, and rocking back and forth are distinctive signs of withholding. The medication history should include the use and efficacy of oral laxatives, enemas, and other medications that potentially influence gastrointestinal motility.

Table 42.2 Alarm signs and symptoms in constipation

Constipation starting extremely early in life (<1 month)
Passage of meconium >48 h
Family history of Hirschsprung's disease
Ribbon stools
Blood in the stools in the absence of anal fissures
Failure to thrive
Fever
Bilious vomiting
Abnormal thyroid gland
Severe abdominal distension
Perianal fistula
Abnormal position of anus
Absent anal or cremasteric reflex
Decreased lower extremity strength/tone/reflex
Tuft of hair on spine
Sacral dimple
Gluteal cleft deviation
Extreme fear during anal inspection
Anal scars

From Tabbers MM, DiLorenzo C, Berger MY, Faure C, Langendam MW, Nurko S, et al. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. J Pediatr Gastroenterol Nutr. 2014 Feb;58(2):258–74, with permission

Alarm Symptoms

To differentiate between FC and constipation with an organic cause, alarm symptoms suggestive for an organic cause should be sought out (Table 42.2) [2]. Alarm symptoms indicative of an organic cause include delayed passage of meconium, a history of bloody stools without the presence of a fissure, failure to thrive, and severe abdominal distension. Furthermore, if parents report smearing of feces, this should raise the suspicion of sexual abuse.

Differential Diagnostic Considerations

Besides organic causes of constipation and devastating causes of FC such as sexual or physical abuse, the differential diagnosis should also include harmless conditions that may be misinterpreted as FC; infrequent defecation in breastfed infants and screaming or crying before or during defecation in infants can be worrying to parents but are often innocuous. Infant dyschezia is a functional gastrointestinal disorder in young children that is defined as straining and crying for at least 10 min before successful passage of soft stools in an infant younger than 9 months of age without any other health problem [32]. Parents report that their child turns red or purple during defecation, but is usually passing soft stools several times daily. This is a self-limiting condition, which does not require any medication or intervention. It is thought to be caused by a lack of coordination between increased intra-abdominal pressure preceding defecation and relaxation of the pelvic floor [33]. Furthermore, approximately 10% of breastfed infants defecate once every 7–10 days, without any other symptom of FC and while still gaining weight normally. This is usually an innocent and self-limiting phenomenon related to breastfeeding and does not require any treatment [34].

Physical Examination

Assessment of weight and height is of key importance since detection of failure to thrive may be a sign of an organic cause of constipation. A physical examination may be helpful in diagnosing constipation and is especially important in detecting alarm signs. It primarily consists of examination of the abdomen, the perianal region, and the lumbosacral region.

Abdominal examination mainly focuses on the detection of a palpable fecal mass or scybala. Perianal inspection should be performed in all children; the physician should look for anatomic abnormalities, perianal feces, fissures, scars, and erythema. The presence of fissures can be a sign of hard or large stools, but can also be a sign of sexual abuse. Hematomas in the perianal region are highly suspicious of abuse. Special attention should be paid to abnormal behavior during physical examination (e.g., sexual acting out, extreme fear) [35]. Although digital rectal examination provides valuable information on the presence of a rectal fecal mass, anorectal sensation, and sphincter tone, it is not necessary for the diagnosis of FC if a child already fulfils 2 or more Rome III criteria (Table 42.1) [2]. If a child fulfils one of the Rome III criteria, a digital rectal examination is recommended since it may help establish the diagnosis of FC. Examination of the lumbosacral region may reveal the presence of a dimple, a tuft of hair, or gluteal cleft deviation, indicative of an organic cause of constipation (e.g., spina bifida).

Laboratory Testing

Laboratory testing (e.g., for hypothyroidism, celiac disease, or hypercalcemia) in children with constipation is only indicated when there is a suspicion for an underlying organic disease, it does not belong in the routine workup of children with FC.

Radiology

Abdominal Radiography

A plain abdominal X-ray is not the appropriate tool to diagnose constipation. The sensitivity and specificity rates are unsatisfactory, and low inter- and intra-observer reliability has been reported for the different scoring systems (Barr, Leech, Blethyn) that are used to evaluate fecal load based on abdominal X-rays [2, 36, 37].

Colonic Transit Time

Although determining colonic transit time can be helpful in the evaluation of colonic motility, there is no evidence to support the routine measurement of colonic transit time in the diagnostic workup of FC [2]. Colonic transit time can be determined with a radiopaque marker test; radiopaque markers are ingested orally and the amount of intra-abdominal markers is then determined using an abdominal X-ray [38–40]. A colonic transit time <62 h is usually considered to be normal [40, 41] (see Chap. 15). An extremely prolonged colonic transit time of more than 100 h indicates a severe form of constipation [40]. Another method to determine colonic transit time is radionuclide scintigraphy; after ingestion of radioactive isotopes, colonic transit is measured with a large-field-view gamma camera. Scintigraphy is a more novel technique than the radiopaque marker test, but its use is less widespread [42–44] (see Chap. 15).

In children with fecal incontinence in whom the diagnosis is not clear, a colonic transit study can be useful to discriminate between FC and functional nonretentive fecal incontinence, a disorder characterized by fecal incontinence without signs of constipation (see Chap. 43) [2, 45].

Contrast Enema

A contrast enema is a useful tool to identify anatomic abnormalities of the anorectum; after infusion of contrast fluid into the rectum an abdominal X-ray is obtained, visualizing the distribution of contrast fluid in the distal gastrointestinal tract. Contrast enemas do not belong in the routine workup of children with FC, but may be useful to detect mechanical causes of constipation (e.g., anatomical abnormalities or complications after colorectal surgery) [46].

Ultrasonography

Transabdominal ultrasonography has been used to measure the transverse rectal diameter [47, 48]. An increased rectal diameter (>30 mm) is often considered to be suggestive for fecal impaction [49, 50]. Although transabdominal ultrasonography is a promising technique for assessment of rectal diameter, there is currently insufficient evidence that the transverse diameter can be used as a reliable predictor of constipation and fecal impaction in children [2, 51].

Manometry

Manometry allows for measurement and quantification of intraluminal pressure and contact force in the gastrointestinal tract; this technique can be utilized to gain insights into gastrointestinal motility.

Anorectal Manometry

Anorectal manometry is a helpful tool in the assessment of anorectal neuromuscular integrity. It can be used to assess the rectoanal inhibitory reflex, anal sphincter pressure, rectal sensation, and defecation dynamics; therefore it is a useful instrument to rule out Hirschsprung's disease and to detect anal sphincter achalasia or dyssynergia [42] (see Chap. 10). The presence of a normal rectoanal inhibitory reflex is considered to be sufficient to reliably rule out Hirschsprung's disease. However, an absent rectoanal inhibitory reflex is not sufficient to diagnose Hirschsprung's disease; this requires confirmation with histochemical evaluation of a rectal biopsy (see Chap. 25). The performance and analysis of anorectal manometry belongs in specialized centers and should not be routinely applied in children suspected of FC.

Colonic Manometry

Colonic manometry assesses colonic motility and can be used to identify colonic neuromuscular disorders (Fig. 42.1a, b). It is often used to guide decision-making in the surgical treatment of FC. This investigation usually includes the following recording periods within one measurement: (1) fasted state; (2) after ingestion of a meal; and (3) after intraluminal administration of a stimulant laxative [16]. Until now, most of the attention has been focused on high-amplitude propagating contractions (HAPCs) [52–55]. The presence of these motor patterns is considered to be an important marker for colonic neuromuscular integrity [56]. With the development of high-resolution colonic manometry catheters, more motor patterns have been identified and their importance in FC is under current investigation [10, 17, 57] (see Chap. 9).

Management

The management of FC in children consists of non-pharmacological and pharmacological treatment modalities. Figure 42.2 represents a treatment pyramid for the management of children with FC.

Education

Education is the first step in the non-pharmacological treatment of FC [58]. This should include an explanation of physiological defecation dynamics, tailored to the developmental age of the child. The negative chain of events that may have been prompted by a painful defecation experience should be explained to parents and, if possible, children. It is important to describe the pathophysiology of overflow incontinence and the pivotal role that withholding behavior plays in this process.

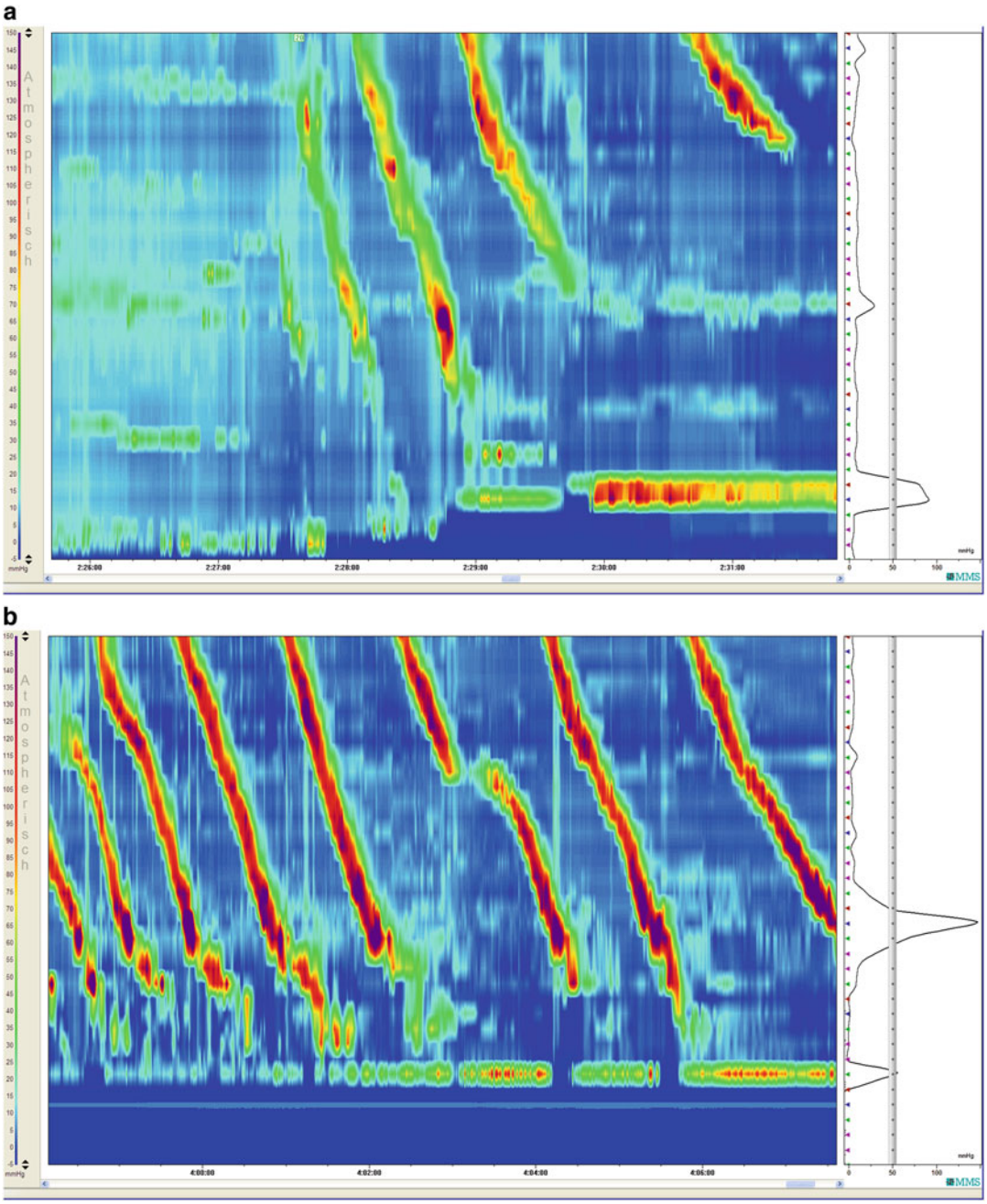

Fig. 42.1 Color plot of a water-perfused high-resolution colonic manometry performed in a 10-year-old girl with functional constipation. The most proximal of the 36 channels is depicted at the top of both figures, the most distal channel at the bottom. Time is represented at the X-axis. The color legend on the *left* represents the amplitude of the contractions. (**a**) After a high-caloric, high-fat meal, several postprandial HAPCs were observed. (**b**) After administration of bisacodyl through the central lumen of the manometry catheter numerous HAPCs were observed, these contractions resulted in stools and flatulence

Toilet Program and Reward System

Because stasis of feces in the rectum can maintain constipation, it is important to evacuate the rectum regularly. In children with a developmental age of ≥4 years, this can be established by introducing a toilet training program, with scheduled toilet sits throughout the day, usually after every meal and after coming home from school. The toilet sits are scheduled after a meal to benefit from the gastrocolic reflex which increases colonic peristalsis upon distension of the stomach. To motivate children to maintain this toilet training program, a reward system can be introduced. By rewarding the child with small gifts for completing toilet trainings, the child is positively reinforced to comply with therapy. A nonaccusatory approach of both physicians and parents

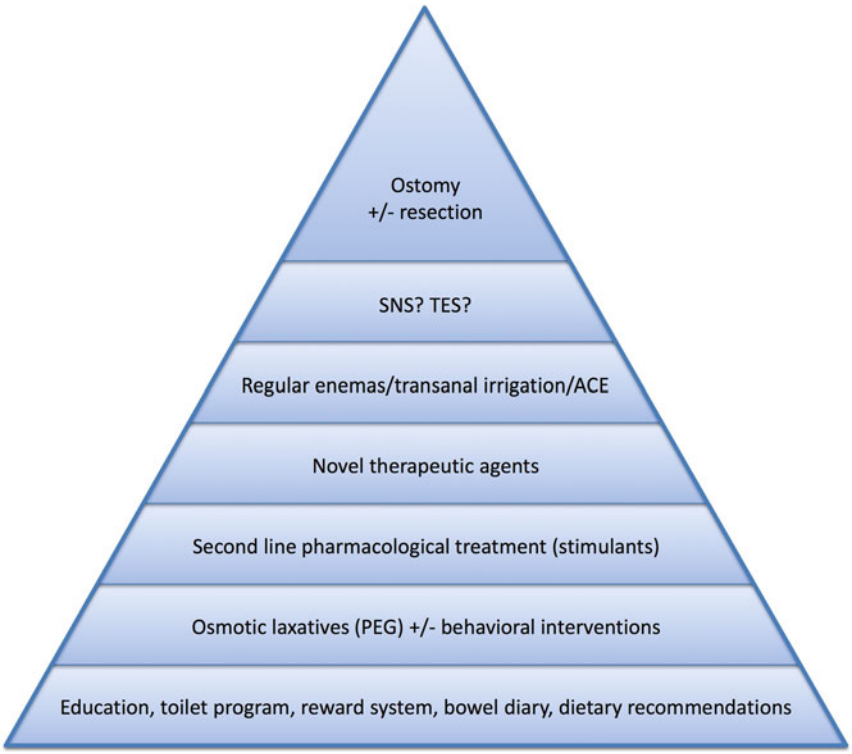

Fig. 42.2 Treatment pyramid for FC. FC is usually treated in a step-up approach, starting with non-pharmacological interventions and osmotic laxatives (PEG) (*bottom* of the pyramid). If these measures are unsuccessful, use of more invasive treatment modalities may be necessary (*top* of the pyramid). Abbreviations: *PEG* polyethylene glycol, *ACE* antegrade continence enemas, *SNS* sacral nerve stimulation, *TES* transcutaneous electrical stimulation

is of key importance since children may feel guilty or embarrassed, especially about episodes of fecal incontinence [58]. Only rewarding periods without fecal incontinence is therefore not recommended, this may increase feelings of guilt and can be experienced as punishment for having fecal incontinence.

Dietary Fiber, Fluid, and Physical Activity

Fiber

Although insufficient fiber intake is associated with FC [59], there is insufficient evidence to support the use of supplementary fiber in excess of the daily recommended intake in children with FC [2, 60].

Fluid

One study assessing extra fluid intake in children with FC showed insufficient evidence for an advantageous effect on constipation symptoms [61]. Therefore, extra fluid intake in children with FC in excess of a normal fluid intake is not recommended [2]. An exception should be made for extra fluid that is recommended for medication intake, such as polyethylene glycol, which needs to be dissolved in water.

Physical Activity

Although physical activity may be associated with a decreased risk of developing FC at the preschool age [62], no studies have been performed to assess the effect of increasing physical activity to treat symptoms of constipation in children [2].

Probiotics

Studies on the use of probiotics have been conducted in children, but to date, there is insufficient evidence to support the use of probiotics in the treatment of childhood constipation [60, 63].

Biofeedback Training

Biofeedback training utilizes reinforcing stimuli in an attempt to achieve a recognizable sensation and encouraging an appropriate learnt response. In theory, this may help children with dyssynergia to adapt their defecation dynamics. However, currently available evidence does not support the use of biofeedback training for the treatment of childhood constipation [64].

Treatment

The pharmacological treatment of FC mainly consists of treatment with laxatives and involves three steps: disimpaction, maintenance treatment, and weaning. The pharmaco-

Table 42.3 Pharmacological management of functional constipation in children

Oral laxatives	Dosage
PEG 3350/4000	Maintenance: 0.2–0.8 g/kg/day in 1–2 doses
	Fecal disimpaction: 1–1.5 g/kg/day (max 6 days)
Lactulose	7 months–18 years: 1–2 g/kg/day, in 1–2 doses
Lactitol	1–6 years: 0.5–1 g/kg/day in 2–3 doses
	6–12 years: 10–30 g/day in 2–3 doses
	12–18 years: 20–60 g/day in 2–3 doses
Bisacodyl	3–10 years: 5 mg/day, in 1 dose/day (at night)
	>10 years: 5–10 mg/day, in 1 dose/day (at night)
Senna	2–6 years: 2.5–5 mg/day, in 1–2 doses/day
	6–12 years: 7.5–10 mg/day, in 1–2 doses/day
	>12 years: 15–20 mg/day, in 1–2 doses/day
Sodium picosulfate	1 month-4 years: 2.5–10 mg/day, in 1 dose/day
	4–18 years: 2.5–20 mg/day, in 1 dose/day
Magnesium hydroxide	2–5 years: 0.4–1.2 g/day, in 1 or more doses
	6–11 years: 1.2–2.4 g/day, in 1 or more doses
	12–18 years: 2.4–4.8 g/day, in 1 or more doses
Rectal laxatives/enemas	Dosage
Bisacodyl	2–10 years: 5 mg/day, in 1 dose/day (at night)
	>10 years: 5–10 mg/day, in 1 dose/day (at night)
Sodium lauryl sulfoacetate	1 month–1 year: 2.5 mL/dose (=0.5 enema) 1–18 year: 5 mL/dose (=1 enema)
Sodium docusate	<6 year: 60 mL
	>6 years: 120 mL
Sodium phosphate	1–18 year: 2.5 mL/kg/dose (max 133 mL/dose)
Lubricants	Dosage
Mineral oil/liquid paraffin	*Oral*
	3–18 years: 1–3 mL/kg/day, 1 or more doses/day (max 90 mL/day)
	Rectal
	2–11 years: 30–60 mL, in 1 dose/day
	>11 years: 60–150 mL, in 1 dose/day

PEG polyethylene glycol

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logical treatment options, including recommended dosages, are summarized in Table 42.3 [37].

Disimpaction, Maintenance Treatment, and Weaning

Fecal impaction occurs in approximately 50 % of children with FC [39, 65]. This fecal mass needs to be evacuated prior to initiating maintenance treatment in order to increase treatment success [66]. Disimpaction can be achieved with enemas or temporary high-dosed oral polyethylene glycol (PEG) (1–1.5 g/kg/day) during 3–6 days [67–69]. High-dose PEG and sodium docusate enemas have been found to be equally effective for disimpaction and although high-dose PEG is associated with a higher risk of fecal incontinence during treatment compared with enemas, PEG is recommended as first choice for disimpaction because it is administered orally [2, 67].

After successful disimpaction, maintenance therapy should be initiated to prevent the re-accumulation of feces [66]. The aim of maintenance treatment is to soften the stools and to facilitate easy and frequent bowel movements. Several laxatives are available for maintenance treatment (Table 42.3). PEG is the oral laxative of first choice in a dosage of 0.2–0.8 g/kg/day. Other therapeutic options are discussed below. Depending on the severity of symptoms, the effect of treatment should be evaluated 1–2 weeks after initiation of treatment. Maintenance treatment should be continued and FC symptoms should be resolved for at least 1 month before considering weaning [2, 37].

Maintenance treatment should be gradually weaned rather than abruptly discontinued in order to prevent a relapse [70]. Weaning can be considered when symptoms are stable for at least 1 month under maintenance treatment, which means that children have a defecation frequency of ≥3 times per week and do not fulfill any other ROME III criteria. It is

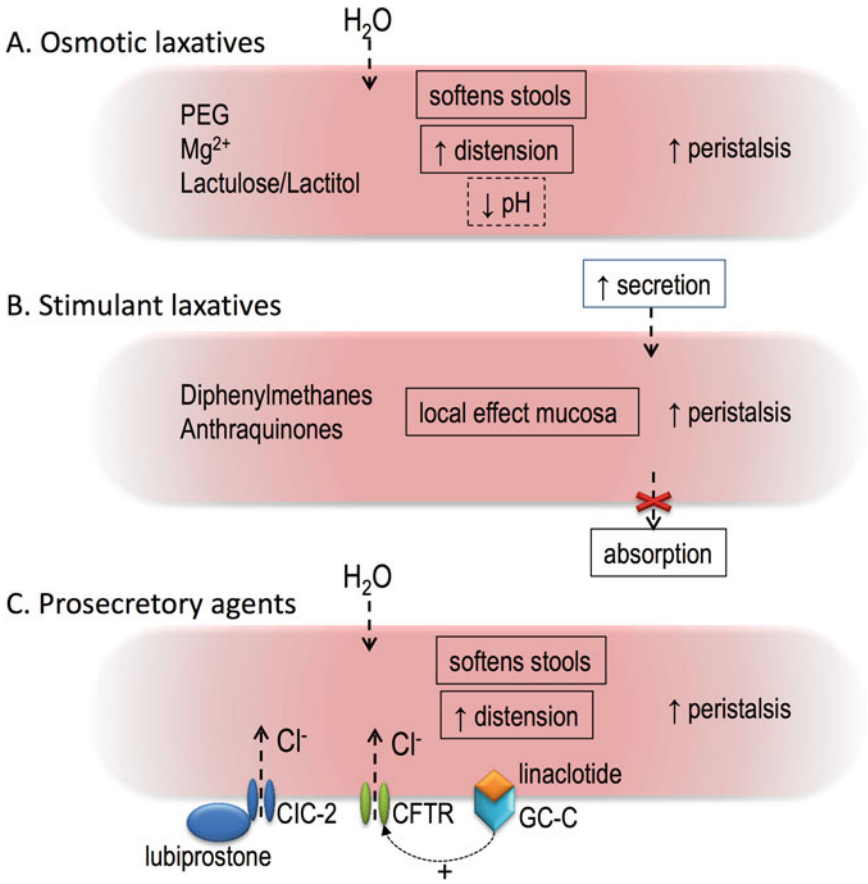

Fig. 42.3 Working mechanisms of different types of laxatives. (**a**) Osmotic laxatives are poorly absorbed by the intestinal wall. This stimulates retention of water in the intestinal lumen, softening the stools, and increasing peristalsis through intestinal distension by increasing stool volume. In addition, fermentation of the disaccharides lactulose and lactitol by intraluminal bacteria results in a decrease in intraluminal pH, which induces an increase in colonic peristalsis. (**b**) Stimulant laxatives are metabolized into active metabolites by intestinal bacteria, these act directly on the intestinal mucosa stimulating peristalsis and influencing fluid regulation mechanisms. Diphenylmethane metabolites exert a local prokinetic effect and stimulate intestinal secretion. Anthraquinone metabolites stimulate colonic motility and water and electrolyte secretion, while they inhibit absorption of water and electrolytes. (**c**) Lubiprostone and linaclotide both promote secretion of chloride-rich fluid in the intestine, softening stools and enhancing stool volume. Lubiprostone is a prostaglandin E1 derivative, which activates chloride channel subtype 2 (ClC-2). Linaclotide activates the luminal guanylin receptor (GC-C), this promotes production of cyclic GMP, which in turn activates CFTR channels

recommended to evaluate symptoms again 2 months after cessation of treatment, to prevent or detect relapses.

Pharmacological Agents

Osmotic Laxatives

Maintenance treatment in children with FC usually consists of oral osmotic laxatives; these agents are poorly absorbed by the intestinal wall, causing osmotic water retention in the intestinal lumen. This softens the stools and increases peristalsis through intestinal distension (Fig. 42.3). Different osmotic laxatives are available, but PEG (macrogol) is the first choice osmotic laxative in children with FC based on its effectiveness and safety profile [37]. PEG is more effective in increasing stool frequency than placebo, lactulose, and magnesium hydroxide [71–74]. Even in young children (less than 2 years of age) the use of PEG has been proven to be effective and safe [74–79]. PEG combined with electrolytes can be prescribed to minimize the risk of disturbing the electrolyte balance due to osmosis (e.g., in young children). However, the addition of electrolytes affects the taste of the medication, which can result in problems with treatment compliance. Most commonly reported side effects include fecal incontinence (especially during disimpaction), flatulence, abdominal pain, nausea, and abdominal bloating.

Two other commonly used osmotic laxatives are lactulose and lactitol, both synthetic derivatives of lactose, which are fermented into hyperosmolar low molecular weight acids by intraluminal bacteria [80]. Both agents result in intraluminal water retention and a decrease in intraluminal pH, which induces an increase in colonic peristalsis (Fig. 42.3). Bacterial fermentation of these agents also induces gas formation, which induces additional intestinal distension and increases peristalsis but may also result in side effects such as flatulence, abdominal pain, and abdominal bloating. Lactulose is less effective than PEG [73], but since it is considered to be safe for all ages, it is recommended in case PEG is not available.

Magnesium hydroxide (also referred to as "milk of magnesia" in its suspension form) is an antacid with an osmotic laxative effect. It is considered to have a lesser effect on defecation frequency than PEG [73]. Side effects of magnesium hydroxide include diarrhea, hypotension, weakness, and lethargy [37].

Stimulant Laxatives

Stimulant laxatives have a different action mechanism than osmotic laxatives, these agents act directly on the intestinal mucosa, stimulating intestinal motility or increasing electrolyte and water secretion (Fig. 42.3). Bisacodyl and sodium picosulfate are diphenylmethanes. In the colon, these nonabsorbable agents are hydrolyzed to their active metabolites, which exert a local prokinetic effect and stimulate intestinal fluid secretion [80]. Bisacodyl can be administered orally and rectally, in the latter form its effect is observed rapidly after administration. Another stimulant laxative is senna, which contains anthraquinones. These agents are also metabolized into their pharmacologically active metabolite by intestinal bacteria [80] and the metabolites stimulate colonic motility and the secretion of water and electrolytes, while they inhibit the absorption of water and electrolytes from the colon. The most common side effects of stimulant laxatives are flatulence, abdominal pain, nausea, and diarrhea.

Lubricants

Mineral oil (or liquid paraffin) is a derivative of petroleum that functions as a lubricant. It is not absorbed by the intestines and may also exert an osmotic effect when it is converted to fatty acids [81, 82]. Two studies compared mineral oil to lactulose [83, 84] and a meta-analysis revealed a significant improvement in stool frequency, although the quality of the evidence was low [73]. Liquid paraffin was also compared to PEG, which revealed no significant difference in treatment response [85]. Liquid paraffin is considered to be safe and effective in the treatment of FC in children [81], but a bothersome adverse effect is leakage of the agent from the anus, causing irritation, itching, and staining of clothing and furniture. Due to incidental reports of the severe side effect of granulomata following absorption and lipoid pneumonia after aspiration [81, 86, 87], liquid paraffin should not be administered to children under 3 years of age [81].

Sodium docusate is a mainly rectally administered lubricant, although oral products exist. Sodium docusate has surface-active properties that induce retention of water in the stools, which gives it its lubricating property [80, 88]. There is no evidence that docusate is effective in pediatric patients with FC. Side effects are seldom reported, but include diarrhea and rectal discomfort.

Enemas

Rectally administered enemas used in the treatment of FC contain chemically active agents that increase gut motility, exert an osmotic effect, or both. They work rapidly, usually within minutes. Different kinds of enemas are available. Sodium lauryl sulfoacetate enemas bring about a redistribution of the water that is bound to feces and thereby soften the stools. These enemas do not have an osmotic effect and are therefore often used in infants. Sodium docusate enemas contain the lubricant docusate (sometimes with added sorbitol, a hyperosmolar agent) and sodium phosphate enemas contain a strong hyperosmolar phosphate solution. Adverse effects of enemas include abdominal pain and anorectal discomfort.

Novel Therapeutic Agents

Lubiprostone, linaclotide, and prucalopride are novel therapeutic agents that have been found to be effective in the treatment of constipated adults [89, 90], but data on the efficacy of these agents in the treatment of FC in children are scarce or not yet available.

Lubiprostone and linaclotide are prosecretory agents, they promote the secretion of fluid in the intestine, thereby softening the stools and enhancing stool volume (Fig. 42.3). Lubiprostone is a prostaglandin E1 derivative that activates the chloride channel subtype 2 (ClC-2), enhancing the secretion of chloride-rich intestinal fluid. Results from a pilot study showed that lubiprostone significantly increases the number bowel movements and that it is well tolerated in children and adolescents with FC [91]. Reported adverse effects included nausea, vomiting, diarrhea, and abdominal pain [91]. At the time of publishing, a multicenter randomized placebo-controlled trial is being conducted to further evaluate lubiprostone as a treatment for FC in children. Linaclotide is a synthetic peptide that activates luminal guanylin receptors on enterocytes, which induces fluid secretion. The use of linaclotide has not been studied in children yet.

Prucalopride is a highly selective serotonergic agent; via activation of 5-HT_4 receptors it increases acetylcholine release resulting in increased gastrointestinal motility [92]. In a pediatric pilot study, prucalopride was shown to have a favorable effect on stool frequency, stool consistency, and fecal incontinence episodes [93]. However, in a subsequent multicenter double-blind randomized controlled trial, prucalopride was not more effective in increasing stool frequency or decreasing fecal incontinence episodes compared to placebo [92]. Reported adverse effects included headache, nausea, abdominal pain, and diarrhea [92].

Transanal Irrigation

Transanal irrigation involves infusion of fluids (usually tap water) into the rectum and colon in a retrograde fashion to mechanically clean out the intestine. This has been shown to be effective in the management of children with neurogenic defecation disorders and anorectal malformations [94–100], but data on the effectiveness of transanal irritation in children with FC are scarce [101]. Transanal irrigations are usually performed with a volume of 10–20 mL/kg of water and the frequency of irrigations depends on the patient's response [94, 101]. In some patients, medications (e.g., stimulant laxatives) are added to the flushing fluids to optimize outcome.

Surgery

In patients with FC unresponsive to medical treatment, surgical treatment may be necessary. Surgical management of intractable FC is currently based on low-quality evidence; there are no guidelines available and the surgical approach may vary between centers [102].

Antegrade Continence Enemas (ACE)

Antegrade continence enemas (ACE) involve colonic irrigation in an antegrade direction through a surgically created access point into the colon, usually at the cecum. The beneficial effect is considered to be due to the mechanically induced propulsion of stools [103]. Commonly applied procedures to achieve ACE are the Malone appendicocecostomy, connecting the appendix to the abdominal wall and creating a valve, and the percutaneous cecostomy, a minimally invasive procedure in which an artificial cecostomy tube connects the cecum with the abdominal wall. Although there is a general lack of prospective studies, good outcomes are estimated to occur in the majority of patients based on retrospective data [102].

Pelvic Floor Surgery

Anal dilatation, anal sphincter myectomy, and intrasphincteric injections with botulinum toxin (botox) have been used in the treatment of FC. By lowering the pressure of the anal sphincter, these treatment modalities aim to facilitate an easier defecation process. Botox injections have a temporary effect and repetitive injections may be necessary to maintain treatment effect. An important downside of these surgical interventions is the risk of fecal incontinence, depending on the type of intervention, this may be permanent.

Colonic Resections

When colonic manometry reveals a dysfunctional colonic segment, resection of the affected segment may be beneficial. This can be followed by subsequent colo-anal or ileo-anal anastomosis or creation of a diverting ileostomy or colostomy. However, the lack of published evidence guidelines makes surgical decision-making difficult.

Electrical Stimulation

Transcutaneous Electrical Stimulation (TES)

Transcutaneous electrical stimulation (TES) is a noninvasive, pain-free form of electrical stimulation that uses interferential current. A promising pilot study in constipated children showed that TES increased bowel movement frequency and decreased the number of fecal incontinence episodes [104]. Subsequent studies have shown a significant effect of TES on quality of life, colonic transit time, and colonic propagating contractions [105–108]. No randomized trial evaluating TES has been conducted in children yet.

Sacral Nerve Stimulation

During sacral nerve stimulation (SNS), the anterior ramus of sacral spinal nerves S3 and S4 is stimulated via surgically positioned electrodes that are connected to an implanted pulse generator. Retrospective pediatric studies suggest that SNS is a promising treatment option in the management of FC [109, 110]. However, randomized-controlled studies with long-term follow-up are essential to gain more insights into the potential role of SNS in the management of FC in children.

Prognosis

The majority of children with FC can be treated effectively with the therapeutic strategies that are currently available. A systematic review of prospective follow-up studies in the hospital setting concluded that within 6–12 months, approximately 50 % of the children recover and are taken off laxatives [111]. An additional 10 % of patients will be asymptomatic on treatment and the remaining 40 % remains symptomatic despite pharmacological treatment [111]. In children with intractable symptoms, unresponsive to medical treatment, symptoms may persist into adolescence or even adulthood despite pharmacological treatment [112–114].

Early adequate therapeutic interventions are of key importance; a delay between onset of symptoms and first presentation at a pediatric gastroenterologist is negatively related to recovery [114].

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Fecal Incontinence in Children

43

Ilan J.N. Koppen and Marc A. Benninga

Fecal incontinence (FI) is defined as the loss of stools in places inappropriate to the social context at least once per month in children with a developmental age of at least 4 years [1]. It represents a difficult and psychologically distressing problem for children and their parents. Soiled underwear can lead to foul smells and may result in bullying and rejection by peers [2, 3]. The involuntary loss of feces often prompts feelings of guilt and embarrassment in both parents and children. This can have a great impact on development, social interactions, and education in affected children [4]. Several studies have shown that FI has a significant impact on the quality of life scores of these children [2, 3, 5, 6]. Moreover, persistence of symptoms into adulthood is associated with impaired health-related quality of life in adulthood [3].

For many years, the amount of feces lost in the underwear was the basis for the differentiation of FI into two types: encopresis and soiling. Encopresis was used as a term to describe expulsion of a large amount of feces, comparable to a normal bowel movement, and soiling referred to the leakage of small amounts of stool. However, these terms have been used interchangeably in medical literature. Therefore the Rome III criteria, which were defined to characterize functional gastrointestinal disorders, have adopted the more neutral term *functional fecal incontinence* rather than the terms encopresis and soiling [1]. This term will also be used in this chapter.

In children presenting with FI without an underlying organic cause, the most important objective is to find out whether FI exists in the presence or absence of constipation or not, and to unravel possible different pathophysiological mechanisms [7–9]. FI can be the result of functional constipation, with fecal impaction causing overflow incontinence [10, 11], or it can exist in the absence of fecal retention, which is classified as functional nonretentive fecal incontinence (FNRFI) [1, 7]. Functional FI in children can also be categorized as either primary, in children who have never been successfully toilet trained, or secondary, in those in whom FI occurs after successful toilet training. It has been proposed that secondary FI is associated with a better outcome after treatment.

Epidemiology

The exact prevalence of functional FI varies depending on the population studied. Bellman, in her landmark study, reported the incidence rate of FI in Stockholm school children to be 2.8 % in 4-year-olds and 1.5 % in 7–8-year-olds [12]. Later, the prevalence of FI was studied in a large population-based study in the Netherlands, where 4.1 % of children aged 5–6 years and 1.6 % of children aged 11–12 years suffered from FI [13]. In a British cohort of 8242 children (age 7–8 years), the prevalence of FI was 1.4 % for children who had at least one episode a week and another 5.4 % for children who were affected by FI less than once per week [14]. In addition, in a retrospective review in 482 children of 4–17 years of age attending a primary care clinic in the United States, the prevalence of FI was reported to be 4.4 % and FI was associated with constipation in 95 % of these children [15]. Unfortunately, most studies do not differentiate between children with constipation-related FI and FNRFI. The only study which assessed the true prevalences of FNRFI and constipation-associated FI, using the Rome III criteria, was an epidemiological survey performed in Sri Lanka. This study reported that 2 % of children (10–16 years) experienced FI; in 82 % of children this was related to functional constipation and the remaining 18 % were considered to have FNRFI [16]. Functional FI was significantly more prevalent in boys (boys 3.2 %, girls 0.9 %), children exposed to recent school- and family-related stressful life events, and

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those from lower social classes [16]. This is in concordance with other studies showing that functional FI is associated with male gender, younger age, a positive family history, non-Caucasian race, important life events such as the birth of a younger sibling, parental discord, a change in living conditions, and other psychological factors [8, 13, 16–23].

Pathophysiology

In approximately 95 % of the children with FI, no organic cause can be identified and these children are considered to have functional FI. Organic causes of FI will not be discussed in this chapter, these include—but are not limited to—anorectal malformations, neurological problems (e.g., spina bifida), and postsurgical complications.

Constipation-Associated Fecal Incontinence

In the majority of children (80–90 %) with functional FI, the loss of feces in the underwear is the result of constipation. Constipation-associated FI is the result of overflow incontinence; small amounts of soft stools pass a hard fecal mass in the rectum, resulting in involuntary loss of stools. This form of FI is often associated with withholding behavior, a key characteristic of functional constipation, especially in younger children. Withholding behavior often occurs after a negative experience such as a hard, painful, or frightening bowel movement [24]. Stool withholding leads to the accumulation of a large fecal mass in the rectum that is difficult to evacuate, also known as fecal impaction (see Chap. 42).

Functional Nonretentive Fecal Incontinence

The remaining 10–20 % of children with functional FI suffer from FNRFI, of which the pathophysiology is incompletely understood. The pathophysiology seems to be complex and is considered to be multifactorial. Historically, functional FI, specifically FNRFI, was seen as a manifestation of emotional disturbance. This idea probably derived from the observation that approximately 30–50 % of children with functional FI are affected by a comorbid emotional or behavioral disorder [4]. Children with functional FI show a heterogeneous pattern of both internalizing and externalizing disorders; high prevalence rates of various anxiety disorders, attention-deficit hyperactivity disorder, and oppositional defiant disorder have been reported [4, 14]. In the mid-1990s it was suggested that children with FNRFI deny or neglect their normal physiological stimuli to defecate and contract the external anal sphincter to retain stool in the rectum. This hypothesis is supported by the normal involuntary anorectal sensorimotor function upon anorectal manometry and rectal barostat testing, whereas abnormal defecation dynamics are often found in these children [7, 25]. A study by van der Plas et al. showed that successful treatment of children with FNRFI normalized scores for behavioral problems [26]. This implies that FNRFI is an important factor in the occurrence and maintenance of behavioral problems in these children. The question whether FI results in behavior problems or vice versa is an important issue and still under debate.

Both day- and nighttime urinary incontinence are commonly found in children with FNRFI, with a reported prevalence of 14–50 % and 20–47 %, respectively [7, 27–29]. Vice versa, 11 % of children with dysfunctional voiding, urge incontinence or bladder overactivity, fulfill the Rome III criteria for FNRFI [28]. It is therefore hypothesized that the concurrence of both urinary incontinence and functional FI in otherwise healthy children without signs of fecal retention might indicate one combined disorder, bladder and bowel dysfunction [30, 31]. This theory is supported by the observation that treatment of urinary incontinence can have a positive effect on FNRFI symptoms and that adequate treatment of FNRFI induces a reduction in the number of urinary incontinence episodes. This indicates a possible neurodevelopmental or behavioral disorder underlying bladder and bowel dysfunction [29, 30].

Compared to children with constipation, children with FNRFI present at the outpatient clinic at a higher age (median age of 9.2 years vs. 6.5 years) and are more likely to have a positive family history (20 % vs. 13 %) [17, 23]. It is unknown why patients visit the outpatient clinic at a higher age and if this is related to the pathophysiology of FNRFI. A possible explanation for this observation is that parents postpone a visit to the doctor because they are ashamed for not being capable of getting their child properly toilet trained.

Organic Causes of Fecal Incontinence

Surgical treatment for Hirschsprung's disease (see Chap. 20) may lead to fecal incontinence in 30–50 % of all patients [32–36]. Other organic causes of fecal incontinence are anorectal malformations (see Chap. 20) and spinal problems.

Spina bifida occurs in approximately 39 in 100,000 births in North America and is typically characterized by paralysis and lack of sensation below the level of the lesion [37]. Global prevalence numbers differ and are influenced by folic acid fortification of a region's food supply. Myelomeningocele is the most common type of open spina bifida and is associated with bowel and bladder dysfunction. Fecal incontinence is common in these children and can exist in either the presence or absence of constipation. The rectoanal inhibitory reflex is usually preserved, but the urge for defecation may be lost and the external anal sphincter is often paralyzed [8]. So when the rectum is filled and rectal distension leads to relaxation of the internal sphincter through the rectoanal inhibitory reflex, there is no mechanism in place to prevent involuntary loss of stools. Spinal problems may

also lead to constipation, which can result in overflow incontinence as well. These children are therefore prone to suffer from fecal incontinence via different pathophysiological mechanisms. Children with spina bifida have been shown to benefit from colonic irrigation, either via the rectum or antegrade through a cecostomy or appendicostomy [38, 39].

Evaluation

A timely and accurate diagnosis is essential for the appropriate treatment of FI. Medical history and a thorough physical examination are often sufficient for an adequate assessment regarding the underlying cause. Only in rare cases, additional tests may be useful.

History

A thorough history needs to elicit the specific symptoms related to the FI episodes. It is important to inquire about the frequency of FI episodes, the situation and time of day when FI accidents occur, accompanying symptoms (e.g., urinary incontinence) and the age of onset of symptoms. The majority of children with FNRFI have FI accidents after school during the late afternoon and before bedtime [7]. To investigate the presence of constipation, questions should address defecation frequency, stool consistency and size, stool withholding behavior, and painful and/or hard bowel movements [1]. Also urinary problems and neurologic deficits need to be evaluated thoroughly. Although rare, one should always be aware of potential organic causes of FI. Because of the high incidence of psychological comorbidities in children with FI, a history on psychosocial and behavioral problems needs to be elicited including inquiry for important life events and sexual abuse [9]. This is a sensitive subject, but it should not be avoided. Furthermore, medical caregivers should be aware that talking about FI may elicit feelings of shame, embarrassment, guilt, and anger in both children and parents and that in some cultures the subject is more of a taboo than in others.

Physical Examination

A thorough physical examination is important to establish or rule out constipation as a cause of FI. Furthermore it is essential to look for alarm signs of underlying organic causes for FI symptoms. To exclude signs of spinal dysraphism it is important to inspect the lower back, perineum, and perianal area. Gluteal cleft deviation has been found to be an important sign of lumbosacral spine abnormalities both in children with functional constipation and FNRFI and should lead to further investigations [29].

Many physicians feel reluctant to perform a digital rectal examination in children and refrain from doing this [40]. However, in children with FI, a digital rectal examination can provide useful information regarding anal sphincter function and neuromuscular integrity. In children who fulfill only one of the Rome III criteria for functional constipation based on medical history, a digital rectal examination is recommended in the most recent ESPGHAN-NASPGHAN guidelines, since in those cases this is essential to establish or rule out the diagnosis of functional constipation (Table 43.1) [41]. In children suspected of FNRFI, a digital rectal examination should therefore always be performed. The perianal region should always be inspected to look for anatomic abnormalities, perianal feces, fissures, hemorrhoids, scars, and erythema. A distinctly wide, open anus, anal scars, or bruises on the buttocks should raise the suspicion of sexual abuse. In children with persisting FI symptoms, the perianal skin may be erythematous or damaged and this may require treatment. Despite the potentially embarrassing feelings this examination may bring about in children, parents, and physicians, examination of the perianal region in the evaluation of functional defecation disorders in children is of key importance and should not be avoided.

Table 43.1 Rome III criteria for functional defecation disorders in children with a developmental age of at least 4 years

Functional nonretentive fecal incontinence	Functional constipation
Must fulfill all of the following for ≥2 months prior to diagnosis 1. Defecation into places inappropriate to the social context at least once per month 2. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject's symptoms 3. No evidence of fecal retention	Must fulfill ≥2 criteria at least once per week for ≥2 months prior to diagnosis with insufficient criteria for the diagnosis of irritable bowel syndrome 1. <3 defecations in the toilet per week 2. ≥1 episode of fecal incontinence per week 3. History of retentive posturing or excessive volitional stool retention 4. History of painful or hard bowel movements 5. Presence of a large fecal mass in the rectum 6. History of large diameter stools which may obstruct the toilet

This table summarizes the differences between these two types of functional fecal incontinence. The only change in Rome IV criteria is the decrease from 2 months to 1 month in the duration of symptoms needed to fulfill the criteria. Hyams et al: http://www.ncbi.nlm.nih.gov/pubmed/27144632

Diagnostic Tests

Functional defecation disorders (functional constipation and FNRFI) are clinical diagnoses that in most cases can be made based on the medical history and a thorough physical examination. In these cases, it is not necessary to perform diagnostic tests before initiation of treatment. Except for determining colonic transit time, which can be useful in differentiating between children with constipation and children with FNRFI, additional investigations are not useful in the routine workup of functional FI. In atypical cases or when conventional treatment fails, additional diagnostic tests should be considered to detect an underlying organic cause [9].

Abdominal Radiography

Multiple studies have shown that there is insufficient evidence to support the use of plain abdominal X-rays as a diagnostic tool in children with functional defecation disorders [42–46]. There is no clear association between clinical symptoms of constipation and fecal loading on abdominal X-rays [46, 47]. Moreover, the sensitivity and specificity rates for the different scoring systems that are used to evaluate fecal load based on abdominal X-rays are unsatisfactory, and low inter- and intra-observer reliability has been reported [46]. However, some physicians argue that if the presence of a fecal mass is uncertain, for example, in a child who is obese, or when rectal examination is not possible due to resistance of the child or when it is considered distressing (e.g., after sexual abuse), an abdominal X-ray may be useful.

Colonic Transit Time

Determining the colonic transit time (CTT) can be a valuable tool in the workup of a child with FI when it is unclear if the child suffers from FNRFI or constipation-associated FI. Currently, the most widely used technique to determine CTT is the radiopaque marker test, which is cost effective and simple to perform [48]. Several days after ingestion of capsules with radiopaque markers, an abdominal X-ray is obtained and the CTT is calculated based on the amount of remaining intra-abdominal markers. Different protocols are in use, with variance in the amount of markers, the amount of study days, and calculations used [48–52]. Based on CTT data in healthy children by Arhan et al., a total CTT exceeding 62 h (mean +2 SD) is considered delayed [49]. In approximately 50 % of constipated children, the CTT is delayed with the majority of the delay occurring in the rectosigmoid segment [53, 54]. In contrast to constipated children, 90 % of children with FNRFI have a normal CTT [7]. Thus, in children with functional FI who do not fulfill the Rome III criteria for functional constipation based on the history and physical examination and who have a normal CTT, the diagnosis should be FNRFI [7]. Therefore, in inconclusive cases, CTT can help to differentiate between FC and FNRFI [9]. In children and adults, a good correlation is found between colonic transit time and symptoms of constipation such as defecation frequency and fecal incontinence frequency [53]. Patients with a severely prolonged CTT (>100 h) have a less favorable outcome at 1 year follow-up [53].

CTT can also be determined by colonic transit scintigraphy, a technique that visualizes the progression of a radiolabeled marker after intraluminal instillation or ingestion. However, this technique is used less commonly in children [52, 55, 56].

Transabdominal Ultrasonography

Transabdominal ultrasonography can be used to measure the transverse rectal diameter [57, 58]. An increased rectal diameter (>30 mm) has been suggested to indicate fecal impaction [59–63]. This is a promising technique that may be used as an alternative for digital rectal examination in the future [59, 61]. However, currently there is insufficient evidence to support the use of the transverse diameter as a reliable predictor of constipation and fecal impaction in children [41, 43].

Magnetic Resonance Imaging

A magnetic resonance imaging (MRI) of the spine is not necessarily required to assess lumbosacral spine abnormalities in the routine workup of children with FI. A prospective study among children with both FC and FNRFI revealed that lumbosacral abnormalities are rarely present and that lumbosacral abnormalities do not correlate with treatment success [64]. Therefore, MRI of the spinal cord should only be performed when there is a clear indication, e.g., abnormal lower extremity findings, midline lower back skin manifestations during neurologic examination, or a suspected neurologic disorder.

Anorectal Manometry and Rectal Barostat

Several techniques can be used to assess anorectal sensorimotor function. Anorectal manometry is especially useful to assess the rectoanal inhibitory reflex (RAIR), anal sphincter tone, and rectal sensation. Although the routine use of anorectal manometry in children with FI is not recommended [9, 65], it may provide valuable information in specific cases. When tested with anorectal manometry, children with FNRFI show normal sensorimotor function and sphincter tone but abnormal defecation dynamics have been reported to be present in ~50 % of patients [7, 66]. These children are often unable to relax the external anal sphincter during defecation, which is thought to be an acquired control mechanism in which after losing the first stool, contraction of the external anal sphincter occurs to retain the rest of the stool [23]. Anorectal manometry can also provide valuable information in children with intractable constipation, especially to rule out Hirschsprung's disease and to detect anal achalasia or dyssynergia (see Chaps. 42 and 25).

Rectal barostat is another technique to assess anorectal function; it utilizes a rectally inserted pressure-controlled inflatable balloon to determine rectal compliance and pressure thresholds for rectal sensitivity. Children with functional constipation have higher rectal compliance than children with FNRFI and healthy controls, causing them to require a larger volume of rectal contents to reach the intrarectal pressure to evoke an urge to defecate [25]. Even after FC patients are in remission, rectal compliance remains increased [67]. At this moment, there is no indication for routinely performing rectal barostat in children with FI, as findings have no clinical implications [9].

Colonic Manometry

Colonic manometry is used to assess neuromuscular integrity of the colon; it can identify motility disorders. Colonic manometry may be useful in the workup of children with FI due to severe intractable constipation, especially to guide surgical management, but does not belong in the routine workup of children with functional FI.

Treatment

Non-pharmacological Management

Education and demystification are the first steps in the treatment of children with FI. It is important to provide information on prevalence, symptoms, treatment options, and prognosis. When discussing the subject of FI, a nonaccusatory approach is key, since this topic may be accompanied by feelings of guilt, shame, and anger in both children and their parents [8, 23, 68].

The most important step in the non-pharmacological management is instituting a toilet program [23, 68, 69]. A toilet program comprises of daily scheduled toilet sits, which last 5–10 min. Toilet sits are usually scheduled after a meal, to take advantage of the gastrocolic reflex, which increases colonic motility upon gastric distension, thereby facilitating defecation. An extra toilet "sit" right after school can be introduced, since most children experience episodes of fecal incontinence in the afternoon. During these sits, it is important that the child tries to become aware of the feeling of urge to defecate; if the child feels an urge, an attempt at defecation should be made. However, there should be no pressure and defecation is not a prerequisite for a successful toilet sit. Toilet sits need to be conducted in a stress-free, positive, and relaxed environment. The aim of these sits is that the child pays attention to the sensory stimuli in the anorectum and learns how to recognize these sensations and how to act accordingly. This should be explained clearly to children and their parents. Additionally, the importance of a relaxed posture needs to be explained and foot support should be provided for small children in order to achieve correct posture.

Maintaining a toilet program may often prove difficult and noncompliance is a considerable problem, especially in children with behavioral disorders. One technique to improve compliance is to let the child fill out a daily bowel diary and to institute a reward system [65]. Filling out the diary provides the child and the parents better insights into the problem and can help to recognize treatment effect and the effect of noncompliance [70]. By giving the child small rewards for the completion of toilet sits, the child can be motivated to maintain the toilet program. However, rewarding periods without FI should be avoided since this can be discouraging, as most episodes of FI occur involuntarily.

Pharmacological Treatment

The pharmacological treatment of constipation-associated FI is described in detail in Chap. 42. In summary, pharmacological treatment consists of disimpaction followed by maintenance treatment, preferably with poly-ethylene glycol, an osmotic laxative. For FNRFI, there is no clear pharmacological treatment. In contrast to the treatment of constipation-associated FI, the use of oral laxatives in children with FNRFI is not indicated [27]. Using oral laxatives may even increase the risk of FI by making the stools too soft to retain. There is anecdotal evidence that loperamide and imipramine could have a beneficial role in the treatment of FNRFI [71, 72]. Loperamide is an opiate receptor agonist, which decreases peristalsis and increases the internal anal sphincter tone; it is hypothesized that it improves sphincter function and thereby prevents involuntary loss of stools. Imipramine is an antidepressant; it functions as an anticholinergic, which decreases motility and increases sphincter tone and may be beneficial for similar reasons as loperamide. However, due to cardiovascular side effects, imipramine should not be given routinely and close clinical supervision is warranted.

Enemas and Rectal Irrigation

Regular evacuation of the rectum may decrease the chance of losing stools in the underwear. In a RCT among FNRFI patients, children received conventional therapy alone or combined with daily enemas for 2 weeks. Clinical improvement was shown to be greater in the group receiving enemas compared with controls during the active treatment period [73]. However, this difference in outcome did not persist throughout the follow-up period, possibly due to the short duration of treatment.

Another method to achieve a clean out of the rectum is transanal irrigation; this technique has been proven to be effective and safe in children with constipation-associated FI and FI with organic causes [74, 75]. However, evidence on the effect of transanal irrigation in children with FNRFI is lacking.

Prognosis

The prognosis of FI is largely dependent on the type of FI: constipation-associated FI or FNRFI. For constipation-associated FI, please see Chap. 42. FNRFI is often a long-lasting problem and treatment be challenging [19]. After 2 years of intensive treatment only 29% of FNRFI patients are cured [17]. Most patients recover before they are adults, but 15% will still suffer from FI problems as they reach adulthood [17]. In all children with FI, regular follow-up is recommended. Children and their parents should be motivated to maintain (non-)pharmacological treatment to prevent relapses. If treatment does not lead to improvement of symptoms, referral to a pediatric gastroenterologist for further evaluation and treatment should be considered.

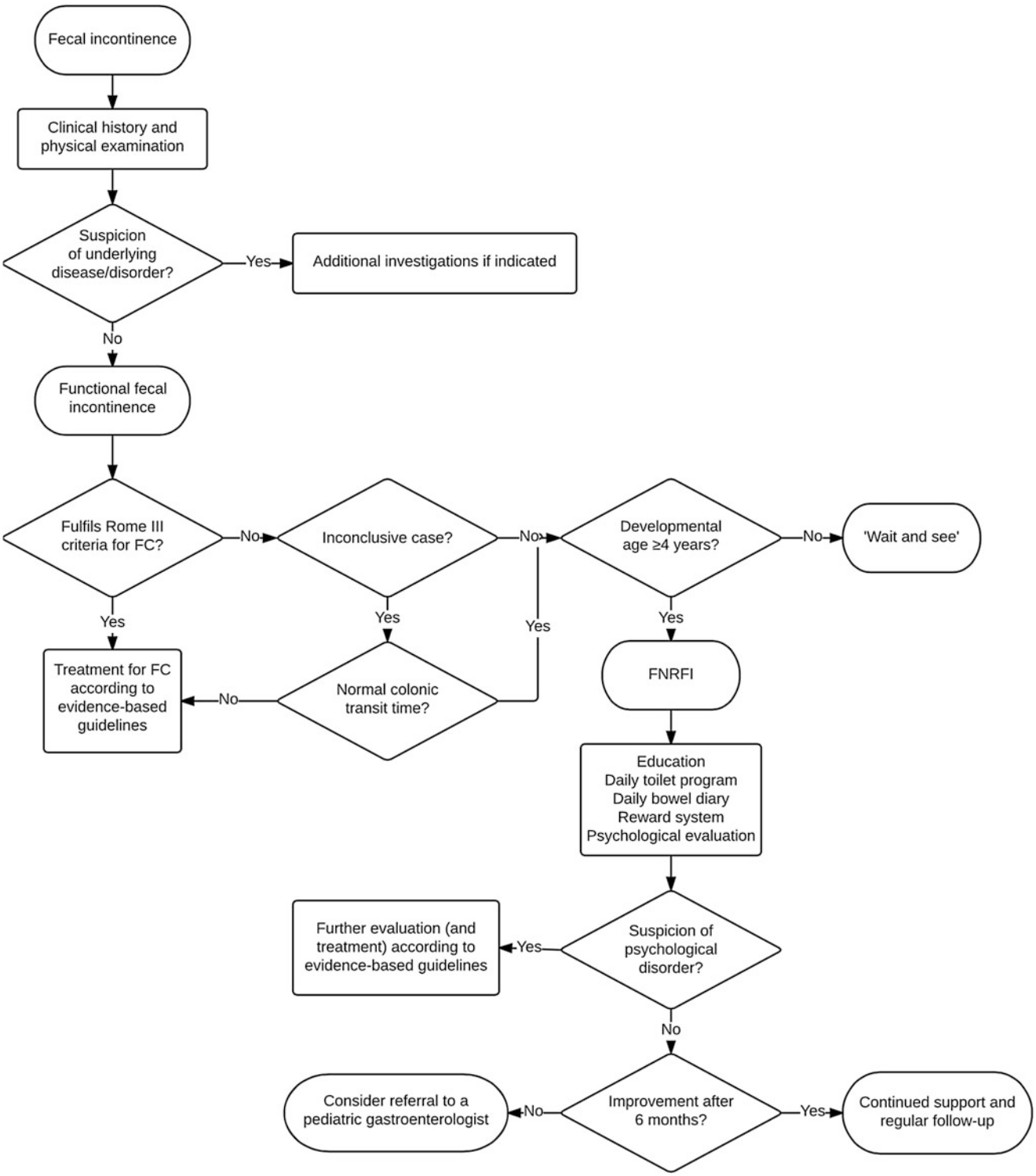

Fig. 43.1 Algorithm for the evaluation and treatment of fecal incontinence in children

Conclusion

FI is a common symptom in children. In the majority of cases this is a functional defecation disorder, either related to functional constipation or as a symptom of FNRFI. A thorough clinical history and physical examination are essential to discriminate between the different underlying entities. An intensive, positive approach is required for successful treatment of FI in children. An algorithm for the evaluation and management of FI is provided in Fig. 43.1.

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Part VI

Treatments

Drugs Acting on the Gut: Prokinetics, Antispasmodics, Laxatives

44

Aileen F. Har and Joseph M.B. Croffie

Disorders of gastrointestinal motility result from abnormal contractions of the smooth muscles of the gastrointestinal tract. This may result in diarrhea and bloating or constipation with or without accompanying abdominal pain. Drugs that act on the gastrointestinal tract may be categorized into three groups: (1) agents that enhance smooth muscle contractions, referred to as prokinetic agents; (2) agents that inhibit contractions, which may be agents that retard normal peristalsis referred to as antimotility agents (opiates and opiate receptor agonists), or agents that reduce abnormally elevated gastrointestinal smooth muscle tone, referred to as antispasmodics (anticholinergics, direct smooth muscle relaxers, and calcium channel blockers); and (3) agents that act to promote evacuation of stool, referred to as laxatives. This chapter will discuss prokinetics, antimotility agents, and antispasmodics, as well as laxatives commonly used in clinical practice.

Prokinetic Agents

Available prokinetic medications generally fall under three groups of drugs: dopamine receptor antagonists, motilin receptor agonists, and 5-Hydroxytryptamine-4 ($5HT_4$) receptor agonists.

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Dopamine-2 (D2) Receptor Antagonists

Domperidone

Domperidone is a peripheral dopamine-2 (D2) receptor antagonist that is used to treat gastroesophageal reflux (GER), gastroparesis, functional dyspepsia, nausea, and vomiting. D2-receptors are located both within the brain and in the peripheral nervous system; however, since domperidone has poor penetration of the blood–brain barrier, most of its effects are derived from its action on peripheral receptors. Domperidone has the ability to cross the placenta and small amounts are excreted in breast milk (2 mg/mL when dosed at 10 mg PO three times daily) [1]. It is rapidly metabolized in the liver and has a half-life of 7.5 h [2, 3]. In the gastrointestinal tract, D2-receptor stimulation leads to inhibition of gastric motility; therefore, D2 receptor antagonists decrease the symptoms of bloating, premature satiety, nausea, and vomiting by accelerating gastric emptying, increasing antroduodenal contractions, and promoting esophageal motility [4]. Domperidone also exerts an antiemetic effect on the chemoreceptor trigger zone, which is not protected by the blood brain barrier. One of the main side effects of domperidone is hyperprolactinemia and it has been used off-label to increase milk production for mothers of preterm infants.

Safety and efficacy of domperidone has not been adequately established for the pediatric population. In children admitted to the hospital for vomiting, compared to placebo and metoclopramide (10 mg), nausea and vomiting were significantly lower using domperidone (30 mg); however this study was conducted for a 24 h period only [5]. A recent Japanese study found no advantage for domperidone combined with oral rehydration solution (ORS) over ORS alone in pediatric acute gastroenteritis [6]. Using domperidone to treat GER in children, a double blind placebo-controlled trial was done on 17 patients [7]; after 4 weeks of therapy, there was a significant decrease in the number of measured postprandial reflux episodes, but no decrease in reported symptoms. The most commonly reported adverse event was diarrhea. Two systemic reviews of pediatric gastroesophageal

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reflux disease (GERD) treatments did not recommend the use of domperidone in this patient population due to lack of data showing its efficacy [8, 9].

In a controlled study of 26 neonates, two doses of domperidone were given during a 24-h combined multichannel intraluminal impedance and pH study [10]. There was a paradoxical increase in the number of reflux episodes, a decrease in reflux duration, and no difference in the maximal proximal extent of reflux or changes in the pH. Oral domperidone in neonates is associated with prolonged QTc interval in patients ≥32 weeks of gestation [11]. Mean QTc prolongation was 14 ms with increasing gestational age and serum potassium at the upper limit of normal being independent risk factors. In 40 premature infants with a gestational age of <34 weeks, there was no statistically significant increase in QTc for up to 14 days after initiation of treatment with domperidone (0.25 mg/kg, every 6 h); two patients did have an abnormal QTc, but with no clinical effects [12]. In a study of 22 pediatric patients under the age of 2 years, the QTc was measured prior to and 1 week after starting domperidone (0.3 mg/kg, 3 times/day) [13]. The mean baseline QTc of 410 ms (350–450 ms) was not statistically different ($p = 0.159$) from the mean QTc while on domperidone of 410 ms (320–560 ms), although two patients did have an abnormal QTc of ≥450 ms.

A systemic review of studies in adults found that approximately 64 % of studies showed that domperidone was effective in improving symptoms of diabetic gastroparesis and 60 % showed efficacy in improving gastric emptying [14]. In cases of GERD without evidence of gastric dysmotility, domperidone does not provide increased benefit to adult patients in comparison to acid suppression alone [15]. For adult treatment of functional dyspepsia, a meta-analysis revealed that there was significant improvement in the patient's global assessment with an OR of 7 (95 % CI 3.6–16); however, there was not enough data to support improvement in gastric emptying [16]. Patients with postoperative nausea as well as nausea from cytotoxic medications have improvement of their symptoms compared to placebo; however in those studies domperidone was given in the intravenous (IV) form, which is no longer available [17–20].

Due to poor CNS penetration, domperidone does not have the neurologic side effects commonly seen with metoclopramide, which is also a D2 receptor antagonist. Domperidone is a CYP3A4 inhibitor and should be avoided in combination with other CYP3A4 inhibitors. There is the potential for prolongation of the QT interval leading to arrhythmias as it acts similar to a class III antiarrhythmic agent. Arrhythmia and sudden cardiac death have been associated with patients given IV domperidone in the setting of hypokalemia and, as a result, the IV formulation is no longer available [21, 22]. Prolonged QTc has been associated with PO domperidone use although this may not lead to adverse events [23]. However, an increased risk of cardiac events associated with oral domperidone use exists when compared to PPI use, metoclopramide use, or nonuse of either medication with increased events for both serious ventricular arrhythmia and sudden cardiac death [24, 25]. Past use of domperidone has not been associated with increased risk of cardiac events. Risk may also be increased in patients older than 60 years, males, receiving higher doses, and in individuals without diabetes [24–26].

Domperidone is available in oral tablet, oral suspension, and rectal formulations. The recommended dosing is 10–20 mg two to four times daily 15–30 min before meals. Pediatric dosing is 0.1–0.3 mg/kg/dose two to four times daily, not exceeding adult dose. Tablets may be crushed and given through gastrostomy, nasogastric, or jejunostomy tubes.

Metoclopramide

Metoclopramide is a dopamine (D2) receptor antagonist that stimulates the stomach and duodenum by causing efferent myenteric cholinergic neurons to release acetylcholine. There is also an increase in the lower esophageal sphincter (LES) tone [27, 28]. Metoclopramide's antiemetic properties are due to its effects on the central nervous system D2 receptors in the chemoreceptor trigger zone. However, due to its ability to cross the blood brain barrier, it also has the potential to cause acute extrapyramidal reactions [29, 30] and tardive dyskinesia with long-term or high-dose use [31, 32]. Metoclopramide is used to treat GER, chemotherapy-induced nausea, postoperative nausea and vomiting, and gastroparesis. Evidence for use in pediatric GER is conflicting as some studies show that there is no significant improvement in symptoms and esophageal pH measurements compared to placebo while others show significant improvement [33, 34]. In the NICU setting, there may be an increased risk for adverse events compared to erythromycin [35]. Metoclopramide is used frequently to treat postoperative nausea and vomiting [36].

Metoclopramide is available in the PO, SC, IM, and IV forms. A nasal spray formulation is currently undergoing clinical trials [37]. The adult dose is 10 mg three to four times daily. The pediatric dose is 0.4–0.8 mg/kg/day divided four times a day not to exceed adult dosage. A black box warning issued by the United States Food and Drug Administration cautions that cumulative use >12 weeks in duration increases risk of tardive dyskinesia, which may be irreversible. Extrapyramidal symptoms occur more commonly within 24–48 h of initiation of therapy and children are at increased risk especially with higher dosing. Pseudoparkinsonism has also been reported and is usually reversible. Other side effects include sedation and hyperprolactinemia. The half-life in children is around 4 h with 85 % being eliminated in the urine, therefore dosing should be adjusted in cases of renal dysfunction. Metoclopramide does cross the placenta, although there may not be teratogenic

effects [38], and it is excreted in breast milk. Onset of action is 15–30 min after oral dosing and 1–3 min after intravenous administration [39].

Motilin Agonists

Erythromycin

Erythromycin is a macrolide antibiotic, but it also acts as a motilin agonist and its primary prokinetic use is for the treatment of gastroparesis. Motilin is a peptide hormone secreted by the small intestine from the enterochromaffin cells [40]. The receptors for motilin are found mainly in the smooth muscle and cholinergic neurons of the gastric antrum and proximal duodenum [41]. The main effect of motilin is stimulation of phase 3 of the motor migrating complexes (MMCs) in the inter-digestive state [41]. Janssens et al. first studied the effect of erythromycin on gastric motility on ten diabetic patients with gastroparesis in 1990 [42]. Compared with placebo, an IV dose of 200 mg significantly improved gastric emptying from a 120 min mean retention of 63 ± 9 to 4 ± 1 %. This preliminary study also showed an improvement in gastric emptying in the same ten patients after 4 weeks of 250 mg, PO, three times daily, but to a lesser degree. Erythromycin may be given through both oral and intravenous routes. Adult dosing ranges from 50 to 250 mg, three or four times a day and pediatric dosing is typically 5 mg/kg/dose. Different motor patterns are elicited from varying erythromycin dosages [43]. Low dose erythromycin (1–3 mg/kg IV) stimulates the neural motilin receptors leading to augmentation of phase 3 of the MMCs [43, 44]. A higher dose of the drug stimulates the smooth muscle motilin receptors leading to sustained contractions in the antrum and antroduodenal coordination [43–45]. Long-term therapy appears to be safe; however, decreased efficacy is seen after prolonged treatment due to downregulation of motilin receptors. There has been no evidence that erythromycin has any prokinetic effect on the colon during colonic manometry studies [46, 47].

Commonly reported side effects include nausea, vomiting, and abdominal pain. There have been reports of erythromycin being associated with serious cardiac arrhythmias and prolonged QTc [48–50]. Erythromycin should not be used concurrently with medications metabolized by cytochrome P450 3A4 (CYP3A4) such as cisapride, terfenadine, pimozide, or astemizole as it is a CYP3A4 inhibitor. Caution must be used in young infants as there is an eight- to tenfold increased risk of developing hypertrophic pyloric stenosis in term or near-term infants when used within the first 2 weeks of life and when the treatment course is >14 days [51]. There is insufficient data in the preterm infant population as to whether there is increased risk of pyloric stenosis and a recent review did not show increased incidence for this particular population for treatment of dysmotility due to immaturity of the gastrointestinal tract [52]; in fact, feeding tolerance may be improved with erythromycin in preterm infants with very low birth weight [53]. Erythromycin is excreted in breast milk at levels ranging from 50 to 100 % of maternal serum levels [54] and should be taken into consideration when treating nursing mothers.

More recently, azithromycin has been considered as an alternative to erythromycin as a prokinetic agent. It has been shown to bind to motilin receptors and to produce contractions similar to erythromycin [55, 56]. There may be greater effect on the duodenum compared to erythromycin with a higher number of MMCs generated [57]. Unlike erythromycin, it is not a CYP3A4 inhibitor so there may be less concern for drug interactions. However, all macrolides have been associated with possible QTc prolongation.

Cholinergic Agents

Bethanechol

Bethanechol is a cholinergic medication, which acts as a muscarinic receptor agonist leading to stimulation of esophageal peristalsis and increased antral contractility. It is also used to treat urinary retention secondary to neurogenic bladder. It causes decreased episodes of esophageal reflux by increasing LES pressure and increasing esophageal clearance [58–61]. Bethanechol's effect on the amplitude and duration of esophageal contractions are more pronounced in the distal esophagus and there is less effect on upper esophageal motility [62]. In patients with normal LES tone and normal esophageal motility, it is questionable whether bethanechol is useful in the treatment of uncomplicated GER and acid suppression may better serve this population [63, 64]. Patients with known esophageal dysmotility and abnormal LES tone, such as those post tracheoesophageal fistula repair or esophageal atresia, may benefit from bethanechol [65]. It improves smooth muscle function in patients with ineffective esophageal motility documented by esophageal manometry [66].

Bethanechol is available by oral and subcutaneous administration only and the onset of action is 30–90 min. It should not be used in combination with anticholinesterase inhibitors. The mechanism of metabolism and excretion is unclear. Pediatric dosing is 0.1–0.2 mg/kg/dose before meals up to four times a day and the adult dose is 10–50 mg two to four times a day. Side effects to note include bronchial constriction and it should be used with caution in asthmatics. Bethanechol produces other cholinergic effects including urinary frequency, miosis, lacrimation, and flushing.

Neostigmine

Neostigmine is a synthetic, reversible acetylcholinesterase inhibitor. It is used in the treatment of myasthenia gravis, bladder atony, and for reversing nondepolarizing muscle relaxants.

Neostigmine has also been used to treat patients with acute colonic pseudoobstruction (ACPO), also known as Ogilvie's syndrome. Its use as a promotility agent has not been well studied in pediatric patients. The first reported case of successful treatment of a pediatric patient with ACPO was in a 4-year-old male with spastic quadriplegia who was 10 days postoperative for bilateral femoral varus derotational osteotomies and botulinum toxin injections of the gastrocnemius muscles [67]. Neostigmine was administered intravenously at a total dose of 0.05 mg/kg over 5 h [67]. In a group of ten pediatric patients with hematologic malignancies who experienced ACPO, eight responded to doses of neostigmine at 0.01 mg/kg/dose administered subcutaneously, given twice a day for no more than five doses [68]. One patient reported diplopia and one reported abdominal pain [68]. In another case report, a 9-year-old boy with cerebellar medulloblastoma on chemotherapy was successfully treated for ACPO with the same subcutaneous dosage after three injections [69]. In a third case report, a 3-year-old girl with sickle cell disease with ACPO had resolution after two doses of neostigmine at 10 mcg/kg [70]. The patient was in vaso-occlusive crisis and had a colon measuring 6.5 cm. She started passing stool within 6 h of neostigmine injection. More recently, the effects of neostigmine on gastroduodenal motility has been evaluated. In adult patients with gastroparesis, intestinal neuropathy/pseudoobstruction, or other upper GI motility disorders, antral and duodenal phasic pressure activity increased after a 1 mg dose was given intravenously [71].

5-Hydroxytryptamine-4 ($5HT_4$) Receptor Agonists

Cisapride

Cisapride is a $5HT_4$ receptor agonist which acts on the myenteric plexus of the bowel wall to stimulate smooth muscle contraction by release of acetylcholine. $5HT_4$ receptors are found throughout the gastrointestinal tract and stimulation causes increased peristalsis as well as intraluminal fluid secretion. Stimulation of the stomach smooth muscle leads to accelerated gastric emptying. Amplitude of esophageal peristalsis as well as resting LES tone is increased [72]. Cisapride also decreases mouth to cecum time and colonic transit time [73].

While cisapride has never been approved for use in children under the age of 12 years, it has historically been used extensively in this population. The consensus statements issued by NASPGHAN and ESPGHAN in 2000 state that cisapride is recommended for pediatric GERD when non-pharmacologic treatment fails, but that the medication does require close monitoring and specific precautions should be undertaken [74, 75]. A 2010 Cochrane Review, however, did not show any difference in symptom improvement or weight gain when compared to placebo [76]. Nine studies comparing cisapride with placebo or no treatment that met inclusion criteria were included in the meta-analysis [77–84]. The authors reviewed five studies comparing results of esophageal pH studies in patients being treated with cisapride vs. placebo, and while there was improvement in the reflux index, there was not significant improvement in the number of reflux episodes and episodes lasting longer than 5 min. Histologic examination of the esophagus was performed in three studies and in two ($n=6$, $n=20$) studies there was no statistical difference between cisapride and placebo [78, 82], however, one study ($n=17$) did have histologic improvement from baseline. Further large-scale studies are needed to assess the utility of cisapride for GERD, though due to limited access, it is unlikely this information will be obtained. Although cisapride may be efficacious in treating constipation, it is not recommended for treatment of standard constipation as the risks do not outweigh the benefits [85].

Availability of cisapride is restricted due to risk of prolonged QTc interval and serious cardiac arrhythmias and it is only available in most countries through limited-access programs. Multiple studies have shown increase in QTc interval in neonates, infants, and children, however, in many of these cases the medication was dosed above the recommended dosing and some were also taking a macrolide antibiotic concurrently [86–90]. Arrhythmias have also been reported ranging from notched *t* waves to torsades de pointes [86, 89, 91]. In a multicenter, double blind, placebo-controlled trial of 49 children (age 6 months–4 years), however, a dose of 0.2 mg/kg given three times a day in patients without cardiac risk factors for a treatment duration of at least 6 weeks did not show a statistically significant increase in QTc interval and no subjects experienced cardiac events [77].

Cisapride is metabolized in the liver by cytochrome P450 into norcisapride. It is eliminated in urine and feces and its half-life is 7–10 h. Adult dosing starts at 10 mg PO two to four times a day 15 min before meals and dose may be increased to 20 mg for efficacy. Pediatric dosing is 0.8 mg/kg/day divided in three to four times a day and not exceeding adult dose. In the case of renal or hepatic failure, 50 % of the recommended dose should be started. It is contraindicated in combination with macrolide antibiotics, azole antifungals, and any drug that prolongs the QT interval. It should be avoided while CYP3A4 inhibitors are being used and grapefruit juice can also increase cisapride serum concentrations. Caution must be taken in infants who are breastfed as mothers may excrete medications in their breast milk that are contraindicated while using cisapride. Patients with known history of prolonged QTc should not be prescribed cisapride and patients with other known arrhythmias need careful monitoring. Electrolyte imbalance, especially potassium, increases the risk of serious cardiac side effects.

In the USA, cisapride is available only under investigational new device (IND) protocols.

Tegaserod

Tegaserod is a 5-hydroxytryptamine-4 ($5HT_4$) receptor partial agonist. It was previously approved for treatment of females ≤55 years of age with constipation-predominant irritable bowel syndrome (IBS) or for chronic idiopathic constipation, however, it was withdrawn from the US market due to an increased risk of cardiovascular events. In an open label study, 22 adult patients with symptoms of upper intestinal dysmotility underwent a 24 h antroduodenal motility study comparing the effects of tegaserod (12 mg PO) and erythromycin (125 mg IV) [92]. Both medications showed significantly increased motility in the antrum, duodenum, and jejunum. There were differences in the timing and where the two medications exerted their prokinetic effects—tegaserod had higher motor responses in the duodenum and jejunum occurring 2–3 h after administration whilst erythromycin had stronger motor effects on the antrum occurring within 30 min of administration. Both tegaserod and erythromycin induced phase III migrating motor complexes (MMCs) in 55 % and 36 % of patients, respectively.

While tegaserod was never approved for pediatric use, it was widely used off-label in many practices. A report on a single center's experience in pediatric patients reviewed 72 patients with a median age of 10 years (1.1–18.3) [93]. Most of these children were treated for functional constipation and the mean follow-up period was 11.3 months (2.3–45.2). Patients reported a statistically significant improvement in bowel frequency and fecal continence. The most common adverse events were diarrhea (20 %), abdominal pain (8 %), and headache (4 %). No cardiovascular events were reported.

Adult dosing is 6 mg, PO, twice daily before meals. Bioavailability is 11 % and decreased by up to 65 % when taken with food [94, 95]. It is metabolized in the liver and 66 % is excreted unchanged in stool and 33 % as metabolites in urine. Use is contraindicated in severe hepatic or renal impairment. Adverse reactions include diarrhea, abdominal pain, nausea, flatulence, headache, and back pain.

Tegaserod was withdrawn from the US market in 2007 due to increased risk of cardiovascular events. It is available only under emergency IND protocol.

Prucalopride

Prucalopride is a highly selective, high affinity 5-HT_4 receptor agonist, which increases colonic motility by stimulating serotonin release leading to giant migrating contractions [96]. Gastro-pyloro-duodenal motility, as well as gastric emptying, is also enhanced in the canine model [97]. A study in healthy adult males replicated the increased gastric emptying as well as acid clearance from the esophagus and decreased proximal esophageal reflux [98]. There was no decrease in LES relaxation or reflux events. Prucalopride is structurally different from previously available 5-HT_4 receptor agonists and, due to its selectivity, the cardiac side effects seen with cisapride and tegaserod have not been reported. Use of prucalopride has mostly been in adult patients with chronic constipation. There are two published studies of its use in children with functional constipation and they came to opposing conclusions. Dosing ranged from a mean of 0.024 [99] to 0.04 mg/kg/day [100] not exceeding the adult dosage of 2 mg daily. Both studies were conducted over an 8-week period and no major adverse events were reported.

In healthy adult volunteers, prucalopride showed accelerated orocecal transit, colonic transit, and total gastrointestinal transit time [101–103]. Treatment of patients with chronic constipation also showed similar improvements in transit times [104–107] and significant increases in spontaneous complete bowel movements, stool consistency, urge to defecate, and quality of life compared to placebo [104, 106–110]. No significant increase in QTc interval has been reported and the most common complaints were abdominal pain, abdominal distension, diarrhea, nausea, back pain, headache, and dizziness [107–109, 111]. Long-term use appears to be safe with sustained response though more recently there have been conflicting results on its efficacy [112–114].

Prucalopride is approved in Europe for use in women with chronic constipation that is not relieved by other laxatives. Recommended adult dose is 2 mg, PO, daily. The half-life is 24–30 h, it is minimally metabolized, and excreted mainly by the kidneys [115]. Dosing for geriatrics (age > 65 years) and those with severe renal or hepatic dysfunction should start at 50 % of recommended dose. Clinical trials are underway for use in males with chronic constipation. In a phase-3 trial, there was statistically significant improvement in achieving at least three spontaneous bowel movements per week, patient rating of constipation treatment, and quality of life [113]. Adverse events in the treatment group vs. placebo were not statistically different.

Velusetrag (TD-5108)

Velusetrag is a highly selective $5HT_4$ receptor agonist. A phase-2 study has investigated the effect of Velusetrag on colonic transit, colonic filling and emptying, and gastric emptying was measured in healthy volunteers and patients with chronic constipation [116]. In this double blind placebo-controlled study, healthy subjects were given 5, 15, 30, and 50 mg of Velusetrag or placebo. Gastric emptying was not affected after a single dose, however there was a significant increase in emptying after 6 days of consecutive treatment for the 15, 30, and 50 mg dosing. Small bowel transit as measured by colonic filling at 6 h was significantly increased after a single dose at 30 and 50 mg, but there was no statistical significance after multiple day dosing. Colonic transit as measured by $t_{1/2}$ of ascending colon emptying and colonic geometric center at 24 h was increased for the 30 and 50 mg doses after a single dose; however, there was no significant increase in colonic transit compared to placebo after multiple

doses. The two study groups reported similar stool consistency, time to first bowel movement, and number of bowel movements in the 24 h after administration. There was an increase in heart rate by 10 bpm at 4 h after ingestion, but no change in blood pressure or EKG tracings. Subjects reported nausea, diarrhea, and headache as the most common adverse events, which was dose related. Only a single treatment study has been published to date. 401 patients were monitored at baseline, then randomized to placebo or 15, 30, and 50 mg of Velusetrag daily for 4 weeks [117]. Patients had mean increases of 3.6, 3.3, and 3.5 SBM/week on 15, 30, and 50 mg, respectively, compared to 1.4 SBM/week for placebo. The most commonly encountered adverse events were diarrhea, headache, nausea, and vomiting. No cardiovascular adverse events were identified.

Other Prokinetic Agents

Octreotide

Octreotide is a synthetic octapeptide that is a long-acting somatostatin analogue used in many disease processes including gastrointestinal bleeding, pancreatitis, secretory diarrhea, chylous leakage, hypoglycemia, and gastrointestinal dysmotility. For the purposes of this section, only the use of octreotide in gastrointestinal dysmotility will be discussed. Somatostatin, studied in patients with normal gastrointestinal motility as well as the canine model, causes inhibition of gastric activity and stimulation of small intestinal phase 3 of the MMCs beginning in the duodenum [118, 119]. It is commercially available for SC, IV, and IM use. Subcutaneous absorption is rapid and IM is released slowly in a depot formulation. Metabolism is through the liver with 32 % unmetabolized excretion through the urine [120]. Half-life is 1.7–1.9 h, but it is 3.7 h in patients with cirrhosis and 3.1 h in patients with renal impairment [94].

Octreotide has been studied in adult patients with scleroderma and pseudoobstruction; subcutaneous octreotide increased the frequency of intestinal MMCs [121]. After 3 weeks of treatment, patients had a reduction in bacterial overgrowth as measured by hydrogen breath testing and a decrease in bloating, nausea, vomiting, and abdominal pain [121]. A single case report described a 12-year-old girl with chronic idiopathic pseudoobstruction who was successfully treated using 50 mcg of subcutaneous octreotide daily [122]. A recent study found that octreotide has no effect on colonic motility [123].

Methylnaltrexone

Methylnaltrexone is a peripheral μ-opiate antagonist that has been used in the setting of opiate-induced constipation [124]. It is a quaternary ammonium derivative of naltrexone and, due to its low polarity, there is reduced penetration of the blood–brain barrier [125, 126]. Opioid-induced constipation is reversed without inducing withdrawal symptoms or decreasing analgesic effect [124, 127, 128]. μ-receptors are found throughout the gastrointestinal tract [129] and stimulation leads to delayed transit and non-propulsive activity [130]. Decreased intestinal secretion as well as increased absorption in the small bowel and colon also contributes to the constipating effect of opioid medications [131].

In treatment of adult patients receiving chronic opioids for nonmalignant pain, doses of 12 mg every day and every other day have been used; both regimens significantly decreased the time to rescue-free bowel movement as well as increased the number of weekly bowel movements compared to placebo [132]. Adults with advanced illness and opioid-induced constipation treated with doses of 0.15 and 0.3 mg/kg had significantly increased rates of rescue-free bowel movements within 4 h of administration compared to placebo [127, 128].

A case report of the use of methylnaltrexone to treat postoperative ileus in a neonate demonstrated success in restoring bowel motility 15 min after a 0.15 mg/kg IV infusion [133]. The infant had undergone two separate exploratory laparoscopies for necrotizing enterocolitis and was on a fentanyl drip for pain control.

A retrospective review of nine pediatric patients (17 months–21 years) with opioid-induced constipation during treatment for incurable cancer showed that 5/9 achieved a bowel movement after the first dose of 0.15 mg/kg [134], 7/9 achieved laxation after more than 1 dose, and 5/9 had continued response with multiple doses. In another study, 15 pediatric oncology patients were given a mean dose of 0.15 mg/kg, for a total of 19 doses [135]. Of the 19 doses, 14 achieved a bowel movement within 4 h. Two other case reports in a 17-month-old and a 3-year-old, both on palliative care for cancer, reported spontaneous bowel movement after a single dose at 0.12 and 0.15 mg/kg, respectively [136, 137]. No major adverse events were reported in any of the above cases.

Methylnaltrexone is available in a subcutaneous form with onset of action between 30 min and 4 h and a half-life of 8–9 h [132, 138, 139]. It is administered every other day with dosing based on body weight (<38 kg: 0.15 mg/kg; 38 to <62 kg: 8 mg; 62–114 kg: 12 mg; >114 kg: 0.15 mg/kg). Excretion is through both urine and feces, primarily as unchanged drug [139]. Side effects include flatulence, abdominal pain, nausea, dizziness, excessive sweating, and diarrhea. Intestinal perforation has been reported with use and it should be used with caution in patients with diminished gastrointestinal wall integrity. Patients with severe renal impairment (creatinine clearance <30 mL/min) should be dosed at 50 % of recommended dosing.

Naloxegol

Naloxegol is a newly approved oral peripheral μ-opiate antagonist for use in opioid-induced constipation not associated with pain control for cancer. It is a PEGylated form of

naloxone and therefore does not cross the blood–brain barrier. Compared to placebo, a 25 mg/day dose produced significantly higher response rates over a 12 week period with the primary end point being ≥3 spontaneous bowel movements per week and an increase from baseline of ≥1 spontaneous bowel movements for ≥9 of 12 weeks and for ≥3 of the final 4 weeks [140].

In adults, Naloxegol is dosed at 25 mg/day and reduced to 12.5 mg/day if not tolerated [141]. Laxatives should be stopped prior to the initial dose. Renal dosing is 12.5 mg/day if CrCl <60 mL/min, but may be increased to 25 mg if tolerated. Metabolism is hepatic through CYP3A and use should be avoided with CYP3A4 strong inhibitors. Time to peak concentration is 2 h and elimination is in the feces and urine with up to 32 % unchanged drug.

Amoxicillin/Clavulanate

In a study of 20 patients undergoing antroduodenal motility testing, administration of 20 mg/kg of amoxicillin/clavulanate into the small bowel induced a duodenal phase III motility pattern in two out of ten patients receiving the medication 1 hour after a meal, and in nine out of ten patients receiving the medication 1 h before a meal [142]. Further studies are needed to determine the role of amoxicillin/clavulanate as a prokinetic agent.

Antimotility Agents

The commonly used agents are the opioid receptor agonists loperamide and diphenoxylate (Table 44.1).

Table 44.1 Antimotility and antispasmodic agents

Medication	Dosing	Notes
Loperamide	Acute diarrhea (first 24 h)	Adult dose acute and chronic diarrhea—first dose 4 mg, then 2 mg after each loose stool, maximum 16 mg daily
	– 2–5 years (13–20 kg): 1 mg three times a day	
	– 6–8 years (21–30 kg): 2 mg twice a day	
	– 9–12 years (>30 kg): 2 mg three times a day—After first 24 h–0.1 mg/kg doses after each loose stool not exceeding initial dose	
	Chronic diarrhea—0.08–0.24 mg/kg/day divided two to three times a day, maximum: 2 mg/dose(PO)	
Diphenoxylate	– 2–5 years—2 mg three times a day	Adult dose 5 mg four times a day
	– 5–8 years—2 mg four times a day	
	– 8–12 years—2 mg five times a day (PO)	
Hyoscyamine	2–12 years—0.0625–0.125 mg every 4 h as needed—maximum daily dose 0.75 mg (PO, SL)	Adult dose—0.125–0.25 mg every 4 h as needed—maximum daily dose 1.5 mg (PO, SL)
		Adult dose—0.25–0.5 mg every 4 h for 1–4 doses only (IV, IM)
Dicyclomine	>6 months old—5 mg, three to four times a day	Adult dose 20 mg, four times a day—may increase to 40 mg, four times a day (PO)
	Children—10 mg, three to four times a day (PO)	Adult IM dose 20 mg, four times a day
Scopolamine	Antiemetic	Adult dose for antiemetic 0.3–0.65 mg/dose every 6–8 h (PO, IV, SC)
	– 6 mcg/kg/dose (maximum 0.3 mg per dose) every 6–8 h (PO, IV, SC)	Adult dose and children >12 years—for motion sickness 10–20 mg every 8 h as needed (PO)
		Adult dose for transdermal patch—1 patch behind the ear every 72 h as needed
Trimebutine	Children >12 years—100–200 mg three times a day (PO)	Adult dose 100–200 mg three times a day (PO)
Mebeverine	Children >10 years—100 mg three times a day (PO)	Adult dose 100–135 mg three times a day (PO) OR 200 mg twice a day (PO modified release)
OnabotulinumtoxinA	Esophageal achalasia	Adult gastroparesis
	– 20–25 U into each quadrant (80–100 U total per treatment)	– 25 U into each quadrant (100 U total per treatment)
	Anal outlet obstruction	
	– 3–6 U/kg/session to a maximum of 100 U divided into four quadrants	
	Chronic anal fissure	
	– 1.25–2.5 units × 2 per session	
Glyceryl trinitrate (0.2 %)	Apply ointment to the distal anal canal twice a day	
Nifedipine		Adult dose 10–20 mg before meals (PO, SL)

Loperamide

Loperamide is a synthetic opioid receptor agonist acting on the μ opioid receptors in the myenteric plexus of the large intestine [141]. It is a peripherally acting agent and does not cross the blood–brain barrier. It has been shown in meta-analysis of randomized controlled trials to be safe and effective in treating acute diarrhea in adults and children [143, 144]. Serious side effects were reported more often in children younger than 3 years old [144]. Loperamide has also been shown in clinical trials to be effective in reducing stool frequency and urgency in patients with diarrhea-predominant IBS [145]. It is available in tablet and liquid suspension. Side effects include abdominal pain and bloating, constipation, sedation, dry mouth, and, rarely, paralytic ileus. This medication should not be used in the setting of acute diarrhea caused by enteric bacterial pathogens such as *Salmonella* and *Shigella* and in acute ulcerative colitis as it can precipitate toxic megacolon. It should also not be used in children <2 years old; indeed deaths have been reported in young children given loperamide to treat acute diarrhea [146].

Diphenoxylate

Diphenoxylate is a synthetic opioid receptor agonist related to meperidine and fentanyl [141]. Like loperamide, it inhibits gastrointestinal propulsion and has been shown to be effective in treating acute diarrhea. Unlike loperamide, however, diphenoxylate crosses the blood–brain barrier and therefore can be habit forming. Atropine is reportedly added to the preparation to reduce the abuse potential [147, 148]. Side effects include sedation, euphoria, lethargy, confusion, respiratory depression, restlessness, hyperthermia, tachycardia, nausea, vomiting, paralytic ileus, and toxic megacolon. Like loperamide, diphenoxylate should not be used in the setting of acute diarrhea caused by enteric bacterial pathogens and acute ulcerative colitis because of potential to precipitate toxic megacolon. Diphenoxylate should not be used in children <2 years old; opiate and atropine toxicity from diphenoxylate-atropine overdosage leading to death has been reported in children <2 years old [149].

Antispasmodics

Antimuscarinics

Antimuscarinics are a class of drugs that work by blocking the action of acetylcholine at postganglionic parasympathetic receptors in the intestinal smooth muscle. They are the most frequently prescribed antispasmodics in the USA (Table 44.1). Meta-analysis of placebo-controlled trials of drugs used to treat IBS confirms the therapeutic benefit of this class of drugs in adults, although many of the trials were reportedly of low quality [150]. Similar studies in children are lacking. The antimuscarinics currently available in clinical practice are derivatives of belladonna, a naturally occurring plant alkaloid, and include drugs such as hyoscyamine, dicyclomine, cimetropium, scopolamine, clidinium, and trimebutine.

Hyoscyamine is the levorotatory isomer of atropine. It is available as oral tablets, extended release tablets, sublingual tablets, oral solutions, elixirs, and drops. It has been used to treat symptoms of colic and IBS [151, 152]. Although commonly used, there are no randomized controlled trials establishing the safety and efficacy of this medication in treating gastrointestinal disorders, particularly in children. Anticholinergic poisoning has been reported in some colicky infants treated with hyoscyamine [151].

Dicyclomine is an m1-specific muscarinic antagonist which has been used to treat symptoms of colic, IBS, and diverticulitis. It has been shown in double-blind studies to be effective in the treatment of infantile colic [153, 154]; however, 5 % of treated infants had side effects [155]. Although commonly used to treat IBS, there are no randomized controlled trials establishing the safety and efficacy of the drug in treating IBS in children. It has been shown in only one study to reduce symptoms of IBS including pain and fecal urgency in adults [156].

Scopolamine (hyoscine) is another m1-specific muscarinic antagonist which has been used to treat various gastrointestinal disorders including IBS and motion sickness [157]. Methscopolamine and butylscopolamine are derivatives of scopolamine which have also been used to treat IBS. Scopolamine was found in a meta-analysis study to offer benefit in the treatment of IBS in adults [158]; however, there are no published randomized controlled studies establishing its effectiveness in treating this condition in children.

Cimetropium is a synthetic derivative of scopolamine which has both antimuscarinic and direct myolytic activity [159]. It has been shown to be more effective than placebo in reducing the duration of crying in children with infantile colic [159] and a double-blind placebo-controlled study in adults showed that it is effective in relieving pain in patients with IBS [160].

Clidinium is a rarely used muscarinic antagonist which is marketed in combination with chlordiazepoxide as a treatment for IBS, although there are no randomized controlled trials showing its safety or efficacy in treating this condition.

Trimebutine is an antimuscarinic drug which also has some opioid agonistic effects; it accelerates gastric emptying and induces premature phase III of the MMCs in the small bowel, but it inhibits colonic motility through its antimuscarinic activity [161]. This drug has been found to be efficacious in the treatment of recurrent abdominal pain and IBS in children and adults. It was found in a meta-analysis study to be effective in the treatment of IBS in adults [158].

Common side effects of antimuscarinic agents include dry mouth, urinary retention, blurred vision, constipation, sedation, and palpitations.

Direct Smooth Muscle Relaxers

Mebeverine and related drugs including alverine, otilonium, and drotaverine [162–164] are not available in the USA but are available in many countries. They are antispasmodics which are believed to be mostly musculotropic. These drugs exert their antispasmodic effect by acting directly at the cellular level of the gastrointestinal smooth muscle. They have been used to treat IBS. A systematic review of several studies in adults found these agents to be efficacious in improving the symptoms of abdominal pain in adult patients with IBS [165, 166].

For many of these antispasmodics, comparison with placebo in clinical trials of patients with IBS showed no significant difference over placebo, perhaps because of a high placebo effect. Only pinaverium and trimebutine reached clinical significance in relieving abdominal pain compared to placebo [167].

OnabotulinumtoxinA (Botox®)

OnabotulinumtoxinA is the drug name for botulinum toxin A. It is used commonly in cosmetic procedures, but is also used to treat strabismus, blepharospasm, muscle spasticity, cervical dystonia, and hyperhidrosis. It has been used off-label to treat esophageal achalasia, gastroparesis, anal fissure, and anal achalasia. Botulinum toxin A is one of seven serotypes of botulinum neurotoxins produced by the anaerobic bacteria *Clostridium botulinum* [168]. The neurotoxin targets the neuromuscular junction and blocks acetylcholine release causing flaccid paralysis.

In a single center report, postoperative follow-up of adult patients treated for esophageal achalasia revealed recurrent or persistent symptoms in 71% of patients treated with endoscopic botulinum injection [169] compared to recurrent/persistent symptoms in 50% of patients who underwent endoscopic balloon dilation and recurrent/persistent symptoms in 30% of patients who underwent surgical myotomy. Thus in this report, patients who underwent surgical myotomy had the most favorable outcome. Treatment with Botox injections has an initial success rate of 70%, however the effect usually lasts 6–12 months and repeated injections are required [170]. There have been conflicting reports on whether prior injection with Botox decreases the effectiveness of a later Heller myotomy or whether it impacts the ease of the procedure [171–174]. A single center reviewed their experience with pediatric patients diagnosed with esophageal achalasia; out of their 33 patients, 7 were treated with Botox [175]. They used 100 U of Botox per session with 25 U injected into each quadrant of the LES. Six of the seven required 2–3 repeated injections and the longest duration of symptom-free period postinjection was 10 months. Four eventually had a myotomy. One case report also reported response for 8 months postinjection in an 11-year-old boy [176]. A single case report of the use of Botox to treat a diabetic, obese adult with esophageal achalasia was complicated by mediastinitis [177]. The development of a sinus tract between the esophagus and gastric fundus has been reported in a 10-year-old girl following her fifth Botox injection for esophageal achalasia [178].

In two studies, pediatric patients treated with Botox injections for anal outlet obstruction (postsurgical repair of Hirschsprung disease and primary internal anal sphincter achalasia) had variable outcomes [179, 180]. The dosage used was 3–6 U/kg/session to a maximum of 100 U. 31–53% of patients had good long-term outcome and 62–89% had initial clinical improvement after a single injection. Complications included pain following the injection and fecal incontinence. In a recent study of 33 children with obstructive symptoms following surgical treatment of Hirschsprung disease who were treated with anal intrasphincteric Botox injection, initial improvement was found in 76% with a medium duration of 4.1 months (1.7–58.8). Long-term response was observed in 49% [181].

Botox injections have also been used to treat chronic anal fissures. At one center, 13 children (age 1–10 years) were given Botox injections in the external anal sphincter under light sedation to treat chronic anal fissures [182]; patients under age 2 years were injected with 1.25 U×2 doses and patients over age 2 years were injected with 2.5 U ×2 doses. Eleven of the 13 patients had resolution of their symptoms within 1 week of treatment and no adverse events were reported. In a systematic review of nonsurgical therapies for chronic anal fissures, Botox was found to be equivalent to topical nitroglycerin in efficacy; however, nitroglycerin itself was only marginally better than placebo [183].

There is a paucity of data on the usefulness of intrapyloric injections of Botox for treatment of gastroparesis. One randomized controlled crossover study of 23 adult patients with gastroparesis showed no benefit of Botox injection (25 U/quadrant; 100 U total) compared to placebo [184]. In a single published retrospective pediatric study of 45 children receiving intrapyloric Botox injection for idiopathic gastroparesis, 66.7% reported improvement with 90% reporting moderate improvement to complete resolution of symptoms. The median duration of response to the initial injection was 3 months (1.2–4.8) [185].

Topical Nitrates

Topical nitrates have been used to treat painful anal conditions. There are three formulations available—mono, di, and trinitrates—all act to relax smooth muscle by stimulating

production of cGMP, irrespective of autonomic innervations [186]. The only topical formulation available in the USA is nitroglycerin, which is a trinitrate. Its most common use in gastroenterology is for treatment of chronic anal fissures.

In children with anal fissures, 0.2 % glyceryl trinitrate (GTN) applied topically to the distal anal canal twice a day resulted in improvement of symptoms by day 10 of treatment and higher rates of complete resolution after 8 weeks compared to placebo and topical lidocaine [187, 188]. However, one study comparing GTN plus oral senna and lactulose with placebo plus oral senna and lactulose found similar response rates, with 84 % healing overall [189]. Concentrations of 0.05 and 0.1 % ointments were also found to be effective for fissure healing after 8 weeks of treatment [190]. Results at 8 weeks of treatment were similar to results using a eutectic mixture of 5 % prilocaine and 5 % lidocaine (EMLA) [188]. Long-term treatment of chronic anal fissure in 31 children using 0.2 % GTN resulted in a 32 % relapse 1 year after treatment and no relapses for 4 years following initial treatment in 68 % [191].

Glycerine trinitrate has also been used to treat proctalgia fugax, which mainly occurs in patients aged 30–60 years [192, 193].

Calcium Channel Blockers

It has been suggested that calcium channel blockers may be effective in the treatment of some gastrointestinal motility disorders because of their ability to relax smooth muscles. Nifedipine and verapamil have been shown to inhibit sigmoid colon myoelectric response to eating in healthy adult volunteers [194] and reduce internal anal sphincter pressures in patients and controls with high resting anal sphincter pressures [195].

Nifedipine has been used to treat disorders of esophageal hyper-motility such as nutcracker esophagus and achalasia in children and adults [196–199]. Nifedipine at a dose of 0.2 mg/kg aspirated from Gelcaps and given every 6 h reduced the amplitude and number of simultaneous contractions and resulted in clinical improvement in two toddlers diagnosed with diffuse esophageal spasms on esophageal manometry [200]. Diltiazem has been used anecdotally to treat diffuse esophageal spasm in adolescents [201]. Verapamil has anecdotally been used to treat antral spasms in children [202]. Pinaverium, a calcium channel blocker which acts selectively on the gastrointestinal tract, has been found to reduce the duration of abdominal pain in randomized, placebo-controlled studies of adult patients with IBS [203, 204].

Peppermint oil is believed to be a calcium channel blocker and has been found to relax the LES in healthy subjects as well as reduce colonic spasms in patients undergoing colonoscopy [205, 206]. It has been found in double-blind randomized controlled studies to be effective in treating children and adults with IBS [207, 208] and in meta-analysis studies of published trials it was found to be effective in the treatment of both adults and children with IBS [209, 210]. A recent meta-analysis of 9 studies including 726 patients found peppermint oil to be superior to placebo for improvement of global IBS symptoms with minimal side effects [211]. Side effects of calcium channel blockers include headaches, lightheadedness, and constipation.

In summary, meta-analysis studies of controlled trials of antispasmodics in the treatment of IBS have found them to be somewhat superior to placebo, at least for the short term, in the management of IBS in both adults and children [150, 158, 212, 213].

Other Antispasmodic Agents

Oral nitrates have been used in adults to treat spastic disorders of the esophagus, although there are no randomized controlled studies supporting their effectiveness [199]. Sildenafil, a phosphodiesterase inhibitor, has been found in a double-blind placebo-controlled study to reduce LES pressure [199]. No studies of nitrates or sildenafil for these purposes have been reported in children.

Laxatives

Laxatives can be divided into osmotic/lubricant laxatives and stimulant laxatives (see Table 44.2). First-line treatment for constipation starts with osmotic/lubricant laxatives followed by stimulants for cases that are poorly responsive to the initial treatment.

Osmotic and Lubricant Laxatives

Lactulose

Lactulose (1-4-beta-galactosidofructose) is a semi-synthetic disaccharide created through the isomerization of lactose [214]. Lactulose increases osmotic load as well as decreases the stool pH thereby increasing colonic propulsion [215]. It passes through the small intestine intact without degradation by disaccharidases and is broken down by bacteria in the colon to produce lactic and acetic acid [216]. Systemic absorption is minimal with majority of excretion through the stool and <3 % excretion in urine. Formulations contain both lactose and galactose so use is contraindicated in patients with galactosemia. Onset of action is 24–48 h and side effects include cramping, abdominal distension, flatulence, diarrhea, nausea, vomiting, and electrolyte imbalances. Long-term use is safe with few reported adverse events [85].

Table 44.2 Laxatives

Therapy	Dosage
Osmotic agents	
Lactulose	– 1–3 mL/kg/day in divided doses
Magnesium citrate	– May use divided doses
	– <6 years—1–3 mL/kg/day
	– 6–12 years—100–150 mL/day
	– >12 years—150–300 mL/day
Magnesium hydroxide	– May use divided doses
	– 1–3 mL/kg/day of 400 mg/5 mL solution
Polyethylene glycol	– 1 g/kg/day
Sorbitol	– 1–3 mL/kg/day in divided doses
Lubricants	
Mineral oil	– 1–3 mL/kg/day
Stimulants	
Bisacodyl	– 3–12 years—5 mg/day
	– >12 years—5–15 mg/day
Senna	– 2–5 years—2.5–7.5 mL at bedtime
	– 6–12 years—5–15 mL at bedtime
Lubiprostone (adult dosing only)	– Chronic idiopathic constipation—24 mcg BID
	– Female IBS with constipation—8 mcg BID

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Magnesium Salts

Magnesium salts are available commercially as magnesium citrate and magnesium hydroxide. All magnesium salts promote bowel evacuation by osmotic fluid retention. Absorption is 15–30 % and excretion is in the urine. Use is contraindicated in patients with renal failure and renal insufficiency as hypermagnesemia is a significant risk. Caution should be used even in patients who do not have renal dysfunction as excessive ingestion can lead to hypermagnesemia in otherwise healthy children [217, 218]. Other side effects include diarrhea, abdominal cramps, flatulence, hypotension, and respiratory depression. There are few studies evaluating the efficacy of magnesium salts in treatment of constipation, however, compared to a bulk laxative, it may produce more frequent bowel movements [219]. Palatability of magnesium may decrease compliance. When compared to polyethylene glycol (PEG) solution over a 12-month period, 95 % of children using PEG were compliant vs. 65 % using magnesium hydroxide [220].

Polyethylene Glycol

Polyethylene glycol is a high molecular weight, non-soluble polymer that acts as an osmotic laxative. Hydrogen bonds are formed between PEG and water, which prevents reabsorption of water in the colon. With increased water retention, stool is thereby softened and its bulk is increased. The onset of action is 24–96 h; excretion is 93 % through feces with minimal systemic absorption and a bioavailability of 0.2 % [221]. Contraindications to PEG include hypersensitivity, ileus, bowel perforation or obstruction, and toxic megacolon.

PEG is available with or without electrolytes added. In general PEG with electrolytes is used for colonoscopy preparation or disimpaction. PEG without electrolytes is more commonly used for daily management of chronic constipation, but has been used in children for colonoscopy preparation as well [222, 223]. High-dose PEG without electrolytes can be as successful as rectal enemas for disimpaction in the pediatric population [224] with highest success for doses of 1–1.5 g/kg/day [225]. PEG is safe and well tolerated for long-term treatment of chronic constipation with few noted side effects [220, 226–229].

Sorbitol

Sorbitol is a polyalcoholic sugar and acts as a hyperosmotic laxative. Absorption is minimal and it is metabolized in the liver mainly into fructose. There is a paucity of studies evaluating the efficacy of sorbitol for treatment of constipation. Compared to lactulose it has similar safety and efficacy in the geriatric population [230]. Excessive ingestion of sorbitol in non-constipated pediatric patients is known to cause loose stool and diarrhea [231, 232]. Side effects include diarrhea, nausea, vomiting, lactic acidosis, and electrolyte imbalances.

Mineral Oil

Mineral oil is a lubricant laxative with minimal systemic absorption and primary elimination in the feces. It is a mixture of hydrocarbons derived from petroleum. The oil lubricates the colon, but it also decreases water reabsorption and softens the stool. It should not be used in infants and patients with swallowing dysfunction since there is a risk for lipid pneumonitis with aspiration [233–235]. Other adverse effects include diarrhea, nausea, vomiting, anal itching, and anal seepage. Chronic use could theoretically decrease absorption of fat-soluble vitamins; however, there is no published evidence to support this [236, 237]. One study showed a reduction in beta-carotene levels after just 1 month of treatment [237].

Stimulant Laxatives

Bisacodyl

Bisacodyl is a diphenolic laxative that stimulates intestinal fluid secretion and motor activity. It induces intestinal fluid secretion by direct action on the enterocyte, activating adenylate cyclase and causing an increase in production of cyclic-AMP [238, 239]. Chloride and bicarbonate ions are actively secreted, while sodium and potassium

are passively effluxed into the bowel. Sodium and chloride are then inhibited from reabsorption back into the enterocyte. Contraction of the colonic smooth muscle is caused by increasing the myoelectrical activity through direct irritation of the bowel wall [240, 241]. Systemic absorption is <5 % with onset of action between 4 and 6 h for oral administration and 0.25–1 h for rectal administration [241, 242]. The small fraction that is absorbed is conjugated by the liver and excreted in urine. Most formulations are enteric coated and should not be administered within 1 h of antacids. Side effects include nausea, vomiting, diarrhea, abdominal cramping, proctitis, and electrolyte imbalance.

Bisacodyl and other stimulant laxatives should be used as second-line agents for patients who are refractory to osmotic/lubricant laxatives [85]. There are no data on safety and efficacy of bisacodyl for treatment of constipation, particularly in the pediatric population [243]; however, there is clear evidence that it accelerates colonic transit and stimulates colonic motor activity [244–246]. Chronic and prolonged use of stimulant laxatives may lead to loss of haustra and anatomic changes in the colon, possibly due to muscular or neuronal injury [247, 248]; it is unclear, however, if this is a true risk of long-term usage of bisacodyl [249].

Senna

The mechanism of action of senna as a stimulant laxative is unclear; however, it may increase production of cyclic-AMP in the colon leading to increased ion secretion and increased peristalsis by direct irritation of the colon [250]. Senna is derived from the plant *Senna alexandrina* and has been used for centuries. Absorption is minimal and onset is 6–12 h after ingestion. Senna is metabolized in the liver and excreted through feces and urine. Reported adverse events include hepatitis, hypertrophic osteoarthropathy, analgesic nephropathy, and melanosis coli, which is reversible. There is poor evidence for development of cathartic colon with long-term use of senna [251]. As with other stimulant laxatives, it is a second-line agent and is used in constipated patients failing first-line treatment. Although it is commonly used, there is a paucity of studies evaluating its efficacy in treatment of constipation [243].

A recent meta-analysis of 18 randomized controlled trials (1643 patients) of osmotic and stimulant laxatives for the management of childhood constipation concluded that PEG preparations may be superior to placebo, lactulose, milk of magnesia, and mineral oil in the treatment of childhood constipation. The analysis also found evidence to support the efficacy of mineral oil. Overall the authors of this meta-analysis found the quality of evidence to be low due to a number of reasons including inconsistency and high risk of bias [252].

Lubiprostone

Lubiprostone is a prostone that acts locally on the gastrointestinal tract by activation of type-2 chloride channels (CIC-2) [253]. It is approved for use in adults with chronic idiopathic constipation and females older than 18 years of age with constipation-predominant IBS. Prostones are bicyclic fatty acids derived from prostaglandin E_1 that do not significantly act on prostaglandin E or F receptors or cause smooth muscle contractions [254]. Activation of the chloride channels increases intestinal fluid chloride concentration and fluid secretion, leading to increased stool passage without causing significant change in serum electrolyte levels [253]. Lubiprostone worsens gastric emptying while accelerating small bowel and colonic transit time in normal adult volunteers [255]. A single published multicenter study of its use in the pediatric population found it to be efficacious and well tolerated in the treatment of childhood constipation [256]. Doses used were 12 mcg daily for children <6 years old weighing at least 12 kg and children age 6–11 years old weighing between 12 and 24 kg, 12 mcg twice daily for children 6–11 years old weighing between 24 and 36 kg, and 24 mcg twice daily for all children at least 6 years old weighing at least 36 kg. Adult dosing is 24 mcg PO twice daily for chronic idiopathic constipation and 8 mcg PO twice daily for constipation-predominant IBS.

Lubiprostone is distributed mainly in the gastrointestinal tract with minimal systemic absorption; it is rapidly metabolized in the stomach and jejunum by carbonyl reductase into the active metabolite M3. 60 % is excreted in the urine and 30 % through the feces. Most common reported side effects include nausea, diarrhea, and headache [257]. There have been no studies on patients with hepatic or renal insufficiency and caution is recommended in these populations. No teratogenic effects have been reported; however, there has been increased fetal loss in the guinea pig model and therefore female patients should have a negative pregnancy test prior to initiation of therapy and be advised on contraception [254].

Linaclotide

Linaclotide is a new guanylate cyclase-C (GC-C) agonist [258] which was recently approved by the FDA (August 2012) for the treatment of IBS-C and chronic constipation in adults. Activation of GC-C leads to activation of the cystic fibrosis transmembrane conductance regulator causing secretion of chloride and bicarbonate into the small intestinal lumen [259]. Visceral hypersensitivity is suppressed by cGMP acting on submucosal afferent pain fibers to decrease nerve reactivity [260] and a decrease in abdominal pain compared to baseline and to placebo has been reported [261]. Doses ranging from 75 to 600 mcg improved bowel habits in men and women >18 years of age with IBS-C [261]. In adult women with IBS-C, colonic transit was improved over a 5-day treatment period with 1000 mcg of linaclotide [262].

For adult patients with chronic constipation, bowel movement frequency, stool consistency, and straining as well as overall quality of life were improved on trials of linaclotide [263, 264]. The approved dose for treatment in adults is 145 mcg QD for chronic idiopathic constipation and 290 mcg QD for constipation-predominant IBS. Clinical trials of linaclotide for treatment of childhood constipation and constipation-predominant IBS are ongoing.

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Drugs that Work in the Brain

45

Paul E. Hyman and Rami Arrouk

A recent systematic review of pediatric randomized placebo -controlled drug trials (RCTs) for functional abdominal pain found only eight studies, low numbers of subjects, and many limitations and biases [1]. The absence of strong scientific evidence supporting drug efficacy has not diminished the enthusiasm for prescribing drugs for pediatric functional gastrointestinal disorders (FGIDs). In this chapter much of the advice comes from anecdote rather than RCTs. One goal of this chapter is to provide a stimulus for research in this area.

Over the past two decades, pediatric gastroenterologists used psychotropic medications for off-label indications. Pediatric gastroenterologists learned about psychotropic medicines from adult gastroenterology RCTs. However, adult data do not assess the risk of long-term effects of psychotropic medicine on the development of the central nervous system (CNS) or enteric nervous system. The possibility of adverse neuro-developmental changes caused by psychotropic medications is reason for caution in treating children. On the other hand, when a daily oral drug suppresses monthly cyclic vomiting episodes, the immediate benefits seem to outweigh unknown long-term risks. Most pediatric gastroenterologists do not collaborate routinely with psychiatrists or other mental health professionals, so it may be beneficial for pediatric gastroenterologists to have knowledge of psychotropic drugs to treat FGIDs. Also, recognizing and treating coexisting psychiatric symptoms may improve both disability and perceived physical discomfort.

The Pediatric Research Equity Act of 2003 mandated that the pharmaceutical industry perform pediatric trials for safety and efficacy after a new drug is approved [2]. A minority of psychotropic drugs has been studied in children and safety data remains inadequate. Psychotropic drugs used for gastrointestinal symptoms in pediatric patients will be "off label" for the foreseeable future. A second goal of this chapter is to review psychotropic medicines used for gastrointestinal symptoms, and review existing evidence for their safety and efficacy in children.

There is a warning about suicidal thoughts and action in adolescents on the package labeling of most psychotropic drugs. Suicide risk may be related to depressed individuals responding to antidepressants with a surge of energy sufficient to execute their suicidal ideas [3]. Before prescribing a psychotropic drug it is important to assess the patient's mood, to query the patient directly about suicidal ideas, and to avoid the use of psychotropic medications and make an immediate referral to a mental health professional if a patient is contemplating suicide [3, 4].

Before prescribing psychotropic drugs or psychological interventions, the clinician must address inaccurate beliefs or expectations of the patients and their caregivers. Some patients and families express skepticism about using psychotropic medication to treat physical symptoms. Moreover, children and families do not want to be labeled as having mental health problems, and fear a stigmatizing effect of a psychotropic drug. For example, some young men may find they are excluded from the military if they have been in psychotherapy or have taken psychotropic drugs during adolescence. It is often necessary to educate families about: (1) the differences between the medical and biopsychosocial models of practice, (2) the role of CNS arousal in sustaining disabling chronic symptoms, (3) the efficacy of psychotropic drugs for functional symptoms and associated disability, and (4) factors known to predict a poor outcome, such as refusal to accept psychosocial influences as a factor in disability and refusal to engage with a mental health professional [5]. The prescriber must provide information about side effects and a rationale that is consistent with patient and family interests, and must dispel the unspoken fears. For example, it is important to reassure children and their families that properly prescribed psychotropic drugs do not alter patient's mind or give rise to addiction, and reduce pain by reducing the sensitivity of pain nerves sending messages from the gut to the

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brain, and by decreasing pain amplification that may occur in arousal centers deep in the brain. It is helpful to emphasize that the doses of tricyclic antidepressants used by pediatric gastroenterologists are less than those used by psychiatrists, and drug effects do not last after they are discontinued. A sizable minority of families will not fill their prescriptions, and will not follow through. Adherence to prescribed medication is a problem.

Who Needs a Psychotropic Drug?

Chronic Functional Abdominal Pain

Treatment for chronic abdominal pain varies with the style of the clinician, patient/family preferences, and availability of the variety of modalities. The clinician needs to establish a therapeutic alliance with the family before the family will accept a symptom-based diagnosis and agree to suspend the search for disease. Treatment of functional abdominal pain disorders should always include reassurance, empathy, and education. Children and families should be assured that the clinician believes that the pain is real. The clinician explains that in children abdominal pain without disease is more common than disease. Although drug treatment is common, cognitive behavioral therapy and hypnotherapy are effective for abdominal pain. The success of psychological interventions, as well as the powerful effect of placebos, demonstrates the complementary influences between the brain and the gut and the importance of the CNS in the pathophysiology of abdominal pain. Thus, there is a rationale for treating with psychotropic drugs, especially when the drugs have desirable effects on the gastrointestinal tract (Table 45.1).

Table 45.1 Mechanisms of action for psychotropic drugs on FGIDs

Central effects
1. Reduces pain perception at the sensory cortex
2. Reduces anxiety, hyper-vigilance, and increased stress responsiveness
3. Treats associated psychiatric disorders—depression, PTSD, somatization
4. Treats sleep disorders
5. Reduces autonomic arousal to prevent CVS and abdominal migraine
Peripheral effects
1. Reduces visceral nociceptive signals
2. May improve diarrhea (e.g., amitriptyline) or constipation (some SSRIs)
3. May relax the gastric fundus (e. g., buspirone, mirtazapine, cyproheptadine)

Adapted from: Grover M, Drossman D. A., Psychopharmacologic and behavioral treatments for FGIDS, McCallum R. W., guest ed. Endosc Clin N Am. Gastrointestinal Motility and Neurogastroenterology 2009;19:151–170, with permission

The clinician's script might sound like this: "You have irritable bowel syndrome. It is not dangerous. It comes and goes. You have many choices about what you can do. First, if IBS is not hampering your life, you may choose to do nothing. Second, you might change your diet to the FODMAPS diet for IBS. Third, you might choose a medical food for IBS: enteric coated peppermint oil or bovine serum immunoglobulin. Fourth, you might choose a pill that you take at bedtime for chronic pain. Fifth, you might choose to learn coping skills to make your pain improve using the thinking part of your brain, a technique called cognitive behavioral therapy. Sixth, you might choose medical hypnotherapy, a kind of hypnosis. All of these modalities have the possibility of helping your symptoms, and you can choose any one or more of them. What would you like to do?"

Chronic Nausea

In the author's experience, when a preteen or teen complains of constant nausea there is a high probability that the cause is unrecognized (or recognized) anxiety. Several psychotropic drugs reduce the nonspecific central nervous system arousal that results in chronic, continuous nausea. Bedtime amitriptyline, mirtazapine, or doxepin may eliminate anxiety-associated nausea. SSRIs have transient but bothersome gastrointestinal side effects which may preclude their use for anxiety-associated nausea. Ondansetron and promethazine are ineffective.

Cyclic Vomiting Syndrome and Abdominal Migraine

Psychotropic drugs are used to prevent and to treat acute episodes of cyclic vomiting syndrome (CVS) and abdominal migraine.

Comorbid Psychological Symptoms

Comorbid psychological distress is associated with disability from pain-associated FGIDs [6]. Psychological distress, in turn, is related to maladaptive coping and an external locus of control.

Sleep Disorders

Sleep disorders affect a majority of children with pain-associated FGIDs [7]. Promptly correcting a sleep problem is a way to gain a therapeutic alliance with a patient suffering from insomnia and chronic pain. Although most drugs and

psychotherapy may take weeks to achieve a measurable effect, sleep disorders can be treated from the initial visit. When the patient's fatigue resolves after restful sleep, they are more likely to accept other suggestions. There is no consensus about which drug to use: melatonin, amitriptyline, doxepin or imipramine, mirtazapine, trazodone, and high dose gabapentin may each be helpful for both chronic pain and disordered sleep.

Classes of Psychotropic Drugs for Pediatric FGIDs

Cyproheptadine

The serotonin (5HT)-1 and H-1 histamine receptor antagonist cyproheptadine is used as a first-line drug by many practitioners due to its favorable side effect profile (Table 45.2). 5HT-1 blockade may improve gastric accommodation, thus improving dyspeptic symptoms and providing more room for a larger meal. In toddlers with poor weight gain cyproheptadine is used to stimulate appetite [8]. At 0.25–0.5 mg/kg/day in two or three divided doses it appears to increase voluntary oral intake in more half those treated for about 3 weeks. Tolerance to appetite stimulation appears after roughly 3 weeks, so when it is used as an appetite stimulant cyproheptadine is cycled: 3 weeks on then 3 weeks off. Cyproheptadine prevents cyclic vomiting syndrome and abdominal migraine in the doses described above [9]. NASPGHAN guidelines suggest trying cyproheptadine before amitriptyline in children <5 years of age because of cyproheptadine's safety and side effect profile when compared to amitriptyline. Also, cyproheptadine is available as a liquid, but amitriptyline must be compounded to liquid form for children unable or unwilling to swallow pills. Cyproheptadine may improve symptoms in children with dyspepsia [10] and other functional abdominal pain disorders [11].

Tricyclic Antidepressants

Amitriptyline and other tricyclic antidepressants (TCAs) have complex anti-nociceptive effects. They inhibit the membrane pump mechanism responsible for uptake of norepinephrine and serotonin, increasing adrenergic and serotonergic activities. Tricyclics inhibit muscarinic cholinergic binding. Amitriptyline's pain-relieving properties are likely to be mediated, in part, by recruitment of the endogenous opioid system acting through delta opioid receptors [12]. One theory is that tricyclics begin a process leading to decreased corticotropin releasing factor secretion, thus reducing autonomic arousal. Low dose tricyclic antidepressants have been used for chronic pain for decades. An adult RCT comparing a TCA to cognitive behavioral therapy showed that desipramine and CBT were equivalent in short-term relief of chronic pain from IBS, and both were better than time spent on IBS education [13]. Another adult RCT compared amitriptyline, escitalopram, and placebo for functional dyspepsia [14]. Amitriptyline was most effective for epigastric pain-type dyspepsia. Escitalopram was no better than placebo. Amitriptyline is used to treat chronic neuropathic pain. In RCTs among children with functional abdominal pain, amitriptyline and placebo were both associated with an excellent therapeutic response [15, 16]. In doses that are a small fraction of the doses required for depression, amitriptyline was shown to reduce chronic pain. Amitriptyline was part of a multidisciplinary approach to treat chronic pain in tube fed, medically fragile infants and toddlers, resulting in subjects moving to oral feeding [17, 18]. For chronic gastrointestinal pain or constant nausea a single daily bedtime dose is standard. Amitriptyline has the greatest anticholinergic and anti-histaminergic effects among the TCAs, inducing sleep and reducing diarrhea in diarrhea-predominant IBS [19]. Other TCAs including imipramine, doxepin, nortriptyline, desipramine, and clomipramine may be less sedating and less constipating, and all reduce chronic pain in rats. Doxepin has the best anxiolytic effects of the TCAs, and is sedating, so for patients with anxiety-associated symptoms, doxepin may be a better choice than amitriptyline. Nortriptyline is the least sedating, least constipating of the TCAs. Doxepin and nortriptyline are sold as liquids suitable for children who cannot swallow tablets. Liquid amitriptyline and the other TCAs require preparation at a compounding pharmacy.

Amitriptyline's anticholinergic and antihistaminic properties result in side effects such as dry mouth, constipation, urinary retention, and sedation. Weight gain is common, because amitriptyline improves postprandial pain, nausea, and early satiety [20]. Less common side effects include muscle stiffness, nausea, nervousness, dizziness, blurred vision, urinary retention, and insomnia. Rare side effects include tinnitus, hypotension, mania, psychosis, heart block, arrhythmias, lip and mouth ulcers, extra pyramidal symptoms, depression, and hepatotoxicity [20]. TCAs can also cause dizziness, peripheral numbness, and tingling and reduce seizure threshold. Medications including serotonin reuptake inhibitors (SSRIs), clonidine, fluconazole, erythromycin, terfenadine, carbamazepine, and phenothiazines compete with amitriptyline for metabolism.

In the author's experience, the usual amitriptyline dose for chronic functional abdominal pain is 1 mg/kg/day up to 50 mg/day. It should be taken an hour or two before bedtime to promote restful sleep. To avoid over-sedation, the first week dose should be 10 mg in patients >50 kg, or one-third to one-fourth of the final dose. Each week the dose can be increased by the starting dose. If the patient responds at a lower dose than 1 mg/kg escalating doses stop, so that the

Table 45.2 Common options for drug treatment of the pain-associated pediatric FGIDs

Functional disorder	Drugs		Dose	Medication class	Side effects	Comments
Cyclic vomiting syndrome	*Prophylaxis*	Amitriptyline	10–50 mg qhs	TCA	Constipation, sedation	Amitriptyline: titrate to effect by 10 mg/week up to 50 mg
		Cyproheptadine	0.25–0.5 mg/kg/day divided bid or tid	Histamine H_1 and $5HT_{2a}$ antagonist.	Fatigue, dizziness	Propranolol: contraindicated in asthma
		Mirtazapine	7.5–15 mg qhs	Tetracyclic antidepressant	Weight gain	
		Propranolol	0.25–1.0 mg/kg/d divided bid or tid	β-Adrenergic blocker	Hypotension, fatigue, bradycardia	
	Acute	Lorazepam	0.05–0.1 mg/kg q6h	Benzodiazepine	Respiratory depression	
		Diazepam (rectal)	0.8–1.0 mg/kg/dose	Benzodiazepine		
Functional nausea and vomiting		Amitriptyline	10–50 mg qhs	TCA	Constipation, sedation	Mirtazapine is safer than Amitriptyline
		Mirtazapine	7.5–15 mg qhs	Tetracyclic antidepressant	Weight gain	
Functional dyspepsia	*Epigastric pain*	Amitriptyline	10–50 mg qhs	TCA	Constipation, sedation	Buspirone: avoid grapefruit juice because it increases its serum concentration. Gastric relaxant
	Postprandial distress	Amitriptyline	10–50 mg qhs	TCA	Constipation, sedation	
		Cyproheptadine	0.25–0.5 mg/kg/day divided bid or tid	Histamine H_1 and $5HT_3$ antagonist	Fatigue, dizziness	
		Mirtazapine	7.5–15 mg qhs	Tetracyclic antidepressant	Weight gain	
		Buspirone	10–60 mg/d divided bid or tid	Azaspirodecanediones	Dizziness nausea, restlessness	
Irritable bowel syndrome	*d-IBS*	Amitriptyline	10–50 mg qhs	TCA	Constipation, sedation	Imipramine is less constipating than Amitriptyline
		Alosetron	0.5–1 mg qd or bid	Anti $5HT_3$	Constipation	Clonidine: monitor BP in clinic visits
		Clonidine patch	0.1–0.3 mg/week	α-Adrenergic agonist	Dry mouth, hypotension, drowsiness	
	c-IBS	Imipramine	25–50 mg qhs	TCA	Sedation	
		Citalopram	10–40 mg/day	SSRI	Diarrhea, nausea	
		Lubiprostone	8–24 mcg qd or bid	Cl channel activator	Nausea	
		Gabapentin	100–800 mg tid	Antiseizure	Drowsiness (rare)	
	IBS with anxiety	Doxepin	25–200 mg qhs	TCA	Sedation	
Abdominal migraine	*Prophylaxis*	Amitriptyline	10–50 mg qhs	TCA	Constipation, sedation	
		Cyproheptadine	0.25–0.5 mg/kg/day divided bid or tid	Histamine H_1 and $5HT_3$ antagonist	Fatigue, dizziness	
		Gabapentin	100–800 mg tid	Antiseizure	Drowsiness (rare)	
	Acute	Morphine	0.1 mg/kg/dose repeat as needed to provide pain relief	Opiate	Respiratory depression, constipation	

Adapted from: Hussain S, Hyman P, Psychotropic medications for pediatric functional gastrointestinal disorders. J Pediatr Gastroenterol Nutr 2014;59(3), with permission

patient receives the lowest effective dose to minimize dose-dependent side effects. Treatment duration for chronic pain or nausea is usually until the symptom disappears plus 6 months, or perhaps until the end of the school year. Pain reduction may take several weeks or even months. Immediate pain reduction likely represents a placebo effect. On the other hand, amitriptyline may improve sleep disturbances from the first doses. Abrupt cessation of amitriptyline is associated with nightmares. Sleep disturbances are avoided by incremental dose reduction over several weeks, in steps similar to dose escalation at the start of treatment.

Amitriptyline in doses similar to those for abdominal pain prevents attacks in patients with cyclic vomiting syndrome [9], abdominal migraine, and migraine headaches [21]. Amitriptyline reduces the number of acute CVS attacks in 80 % of affected children, the highest prevention rate of the drugs used for prophylaxis.

In contrast to the routine use of amitriptyline in adults and older children, there is a lack of anything but retrospective, uncontrolled data on the use of amitriptyline in infants and toddlers. Although studies using amitriptyline to treat visceral pain in infants and toddlers showed promise [17] and pain is believed to be a contributor to some children with chronic food refusal [18], one small RCT showed no effect of 1 mg/kg/day amitriptyline in the transition from tube to oral feeding [22]. In that study serial electrocardiograms over 24 weeks revealed no changes in heart rate, P-R interval, QRS duration, or QTc interval.

In the author's experience, amitriptyline frequently resolves long-term fecal incontinence following successful surgery for Hirschsprung's disease.

Amitriptyline overdose is associated with serious cardiac arrhythmias and death. On the other hand, at doses 1 mg/kg/day used to treat chronic pain and nausea, there have been no reports of death or cardiac arrhythmias in over 60 years. In the author's opinion, an electrocardiogram before starting a TCA is unnecessary in otherwise healthy children and adolescents, but may be advisable in those with a personal or family history of QTc prolongation or a history of heart disease. In a risk-prevention study involving 760 children with functional abdominal pain, the risk of true prolonged QT interval was no greater than that of the normal population [23, 24]. However, electrocardiograms picked up cases of prolonged QTc interval and Wolf–Parkinson–White syndrome in unsuspected children and the drug was avoided in those children. If there are cardiac safety issues, it is advisable to choose a different psychotropic medication or mode of therapy.

Serotonin-Receptor Inhibitors

Serotonin-receptor inhibitors (SSRIs) increase the extracellular level of serotonin by limiting its reabsorption into the presynaptic cell, increasing the level of serotonin in the synaptic cleft available to bind to the postsynaptic receptor. SSRIs have weak affinity for the norepinephrine and dopamine transporters, and weak anticholinergic effects. Because they have efficacy equal to the tricyclics, but fewer side effects at doses that treat depression, and safer with overdose, SSRIs are first-line drugs for depression and anxiety. SSRIs include fluoxetine (Prozac), citalopram (Celexa), escitalopram (Lexapro), fluvoxamine (Luvox), paroxetine (Paxil), and sertraline (Zoloft).

Meta-analysis of RTCs in adults suggested that SSRIs were equivalent to tricyclic antidepressants in symptom relief in IBS, followed by larger studies showing usefulness of SSRIs in IBS [25]. In children there was a single RCT with a small sample size showing citalopram superior to placebo in IBS [26]. SSRIs may be used in combination with TCAs, for example, amitriptyline at bedtime to treat pain and facilitate sleep, with non-sedating fluoxetine for anxiety and/or depression in the morning. SSRIs compete with TCAs in degradation pathways, so using them simultaneously will increase serum concentrations of both.

Serotonin receptors are found in brain and gastrointestinal tract, so it comes as no surprise that most side effects from SSRIs are gastrointestinal. Transient diarrhea, nausea, and constipation are common with all of the SSRIs. Gastrointestinal side effects may be minimized by beginning treatment at low doses and advancing slowly, over weeks and months. Responses to each SSRI may differ in the same patient, so that clinicians should not feel limited to one SSRI. It may benefit patients who find one SSRI intolerable or ineffective after a suitable trial of 6–8 weeks to switch to another SSRI, mirtazapine, or buspirone.

Some clinicians obtain an EKG assessing QTc interval prior to initiating citalopram doses >20 mg daily, the usual maintenance dose. There appears to be an increased risk of cardiac arrhythmias at doses >40 mg daily.

Mirtazapine

Mirtazapine is a noradrenergic and specific serotonergic antidepressant. Structurally, mirtazapine is classified as a tetracyclic antidepressant. One RCT in dyspeptic adults showed mirtazapine improved early satiation, quality of life, gastrointestinal-specific anxiety, nutrient tolerance, and weight loss [27]. In adolescents, mirtazapine helped chronic vomiting by reducing nausea, early satiety, and postprandial fullness [28]. It is effective for children with social phobia [29] and for reducing panic attacks. Mirtazapine is a good choice for chronic nausea as it has only a few drug interactions, unlike amitriptyline. At 7.5 mg mirtazapine's antihistamine H-1 effects dominate the side effect profile, and mirtazapine is sedating. It is taken at bedtime to improve sleep. At 15 and 30 mg mirtazapine is less sedating. At higher doses than 7.5 mg alpha-2 adrenergic presynaptic receptor

blockade leads to increased norepinephrine neurotransmission, so that there is a balance of sedating and activating influences. Recently, mirtazapine seemed effective prophylaxis for CVS [28]. Weight gain is a common side effect. Sedation is less common. Overdoses are rarely fatal. Mirtazapine has few drug–drug interactions and no risk for heart-related side effects.

Buspirone

Buspirone is an anxiolytic used alone or in combination with SSRIs or TCAs. It acts via non-benzodiazepine γ-aminobutyric acid receptors. It has strong affinity for 5-HT1 and 5-HT2 receptors and moderate affinity for D2 receptors.

In adults the anxiolytic buspirone reduced symptoms of dyspepsia presumably by improving receptive relaxation of the stomach as well as through CNS effects [30]. Buspirone may increase gastric receptive relaxation and improve symptoms, or augment therapy with antidepressants in adolescents. It was effective in children and adolescents with anxiety disorder [31].

Second Generation Antipsychotics

Second generation antipsychotics (SGAs) are powerful drugs usually reserved for treating psychosis. However, in low doses an SGA may be a useful adjunct to induce and maintain sleep and reduce severe anxiety. Quetiapine is an antipsychotic with complex effects related to dopamine, alpha-2 adrenergic, and serotonin antagonism. It appears to reduce suicide risk in agitated depression. In nonverbal developmentally delayed children who appear to be in great distress, risperidone may be effective in calming both patient and family [32]. Usually low doses (0.2–0.5 mg/dose twice daily) suffice. Metabolic and neurological side effects occur in children treated with SGAs. The risk of weight gain, increased body mass index, and abnormal lipid levels is greatest with olanzapine, followed by clozapine and quetiapine. The risk of neurological side effects including dysphoria and extrapyramidal symptoms is greatest with risperidone, followed by olanzapine and aripiprazole [33].

Gabapentin

Gabapentin is a lipophilic structural analogue of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). Gabapentin is an anticonvulsant used to treat neuropathic pain, generalized anxiety disorder, social anxiety, and panic attacks. Gabapentin works on voltage-sensitive calcium channels to reduce excessive neuronal activity and neurotransmitter release. In post-marketing assessments it appeared to improve chronic pain in about one-third of those taking it [34]. It relieved chronic irritability in nonverbal children, perhaps by reducing pain or dysphoria [35]. For infants and toddlers treated with 10 mg/kg/dose BID or TID, side effects are uncommon. Side effects include dry mouth, nausea, tiredness, clumsiness, or dizziness. Serious side effects are rare. In anecdotes it improved early satiety in infants after cardiac surgery [36] and in infant colic. Infants and toddlers with presumed dysphagia or dyspepsia after unusual pain experiences are treated with 10 mg/kg/dose BID and advanced to TID if there are no side effects. There are no long-term safety data concerning the effects of gabapentin on brain development.

Alpha-Adrenergic Agonists

Clonidine is an alpha-adrenergic agonist used for patients with abdominal pain who exhibit additional psychosomatic symptoms [37]. In adults, clonidine improved diarrhea-predominant IBS [38]. It reduced gastrointestinal symptoms from narcotic withdrawal. Common side effects include dry mouth, drowsiness, dizziness, and tiredness. Because of clonidine's antihypertensive properties, it is appropriate to check blood pressure at each clinic visit and at any time new symptoms associated with hypotension occur.

Clonidine alone or in combination with midazolam was shown to be beneficial in aborting episodes of cyclic vomiting in a few pediatric cases [39, 40].

Benzodiazepines

Short-acting benzodiazepines (BZDs) (e.g., midazolam, diazepam) provide sedation and amnesia for minor procedures [41]. Procedures and treatments may precipitate medical post-traumatic stress disorder when patient comfort is not a priority, and patient anxiety goes unrecognized. For example, placement of a nasogastric tube or an intravenous catheter by a novice and without sedation might cause an unnecessary pain experience. Oral or nasal midazolam and an experienced clinician help the child to cope with unavoidable trauma. There are development-dependent signs and symptoms for childhood post-traumatic stress disorder, and evidenced-based trauma-focused treatment is indicated for children who remain highly distressed or impaired [42].

There is no role for short-acting BZDs for chronic problems like abdominal pain or nausea.

The goal of treatment for acute CVS is to relieve suffering, which is accomplished in most hospitalized patients with the long-acting IV BZD lorazepam titrated to restful sleep. For families who elect to stay home, repeated doses of rectal diazepam are the best option. Rectal diazepam is about

50 % bioavailable, so 0.8–1.0 mg/kg/dose may be necessary. Respiratory depression is a risk, so parents must be carefully instructed on dosing. The goal at home is still restful sleep until the vomiting episode is over.

There is only anecdotal evidence that BZDs may have beneficial effects in disabled abdominal pain patients with comorbid anxiety disorders. Occasionally clonazepam 0.25–0.5 mg BID may be helpful for anxiety relief over a week or two, while waiting for a SSRI to take effect. An advantage of clonazepam over TCAs and SSRIs is that clonazepam works immediately. The addiction potential, worsening of associated depression, and poor safety profile of benzodiazepines make them unattractive. Chronic BZD use is associated with drug tolerance and drug dependency.

Serotonin/Norepinephrine Reuptake Inhibitors

Duloxetine, venlafaxine, and milnacipran are drugs which increase synaptic serotonin and norepinephrine. Both are approved by the US Food and Drug Administration for treating adults with fibromyalgia, and there is anecdotal evidence for improvement in symptoms with other chronic pain disorders. No RTCs have investigated serotonin/norepinephrine reuptake inhibitors (SNRIs) for FGIDs.

Opiates

There is no role for opiates in the treatment of chronic pain or nausea. Intravenous opiates are necessary to relieve pain during acute episodes of abdominal migraine. Intravenous opiates should be titrated to restful sleep for the patient. Codeine is a cause for constipation and sphincter of Oddi malfunction-induced pancreatitis [43].

Melatonin

Melatonin (*N*-acetyl-5-methoxytryptamine) is an endogenous hormone secreted from the pineal gland which plays a role in regulation of circadian rhythms. Exogenous melatonin taken at bedtime can initiate sleep. There is a great deal of evidence that melatonin is effective in a majority of healthy children, in doses between 3 and 10 mg an hour or two before bedtime [44]. Melatonin is the safest of drugs used to initiate sleep. It does not sustain sleep, but after night waking a patient may repeat the dose without risk.

Trazodone

Trazodone is an antidepressant, serotonin antagonist, and reuptake inhibitor. Trazodone is used sporadically in children to treat chronic pain conditions such as fibromyalgia, migraine headache, and to improve sleep, but without RTCs to support its use for those indications in children or adults.

Diphenhydramine

The H1-histamine receptor antagonist diphenhydramine is prescribed for sleep more than any other drug, but there is evidence of frequent paradoxical excitation, next day fatigue, drowsiness, and impaired cognition, and tolerance develops quickly to antihistamines, including diphenhydramine [44]. Diphenhydramine is a poor choice for treating disordered sleep.

Phenothiazines

Phenothiazines were a mainstay of treatment for acute, severe vomiting in the past. Newer drugs are safer, and have a better side effect profile. For cyclic vomiting episodes and familial dysautonomia vomiting crises, long-acting benzodiazepines are a better choice than phenothiazines, including chlorpromazine, prochlorperazine, and promethazine.

Combination Psychopharmacotherapy

Patients with difficult-to-manage FGIDs may benefit from treatment with more than one drug. Examples might include amitriptyline at bedtime to treat chronic pain and facilitate sleep, and an SSRI or mirtazapine in the morning [45]. For anxious children with dyspepsia, there is a rationale for buspirone before meals and mirtazapine at bedtime, because both have relaxing effects on the gastric fundus. For children with pain-associated disability syndrome, a first step of improving sleep with amitriptyline or mirtazapine changes the patient's outlook from one of hopelessness to one of accepting the possibility of positive outcome. Cognitive behavioral therapy takes weeks before it is effective, whereas some drugs have a more rapid onset, especially for inducing restorative sleep. Augmentation might include two different antidepressants, antidepressant plus atypical antipsychotic, or antidepressant and gabapentin. For example, when amitriptyline 50 mg or mirtazapine 7.5 mg qhs are ineffective, sleep may be restored by adding quetiapine 50 mg, and increasing by 50 mg/night until the desired response is achieved.

Pediatric gastroenterologists should familiarize themselves with the most common drug choices for each FGID. Figure 45.1 demonstrates the hierarchy of psychotropic drugs used for FGIDs. All pediatric gastroenterologists should have a working knowledge of amitriptyline, gabapentin, and mirtazapine. Neurogastroenterologists are likely to develop familiarity with clonidine, SSRIs, and buspirone. In the most complicated patients requiring combination therapy or second generation antipsychotics, it is a good idea to consult or collaborate with a psychiatrist or prescribing psychologist [46].

Medication Nonadherence

The most common cause of treatment failure is not taking medicine as prescribed. It is estimated that about 30 % of prescriptions are never filled, a testament to the hopelessness patients and families feel when physical symptoms coexist with anxiety, depression, catastrophization, and helplessness.

There are a number of reasons for nonadherence. The first problem is the delayed onset of psychotropic medicine effects. Many psychotropic drugs, most notably SSRIs, take weeks before there is symptom improvement. It taxes a patient's and family's patience waiting for improvement. Depressed and hopeless patients prematurely decide that the drug is not working. They stop the drug and do not communicate with their clinician. Often they are lost to follow-up.

Next, side effects often lead to medication discontinuation. For example, with amitriptyline, sedation that facilitates restful sleep may spill over into the daytime, creating fatigue and a sense of weakness. If there are open lines of communication, the clinician may decrease the dose for a week so that the patient develops a tolerance to the sedating effects, and ask the patient to take the drug earlier in the evening, or even switch to a less sedating tricyclic like imipramine. With the activating SSRI fluoxetine, the first dose in an anxious patient may cause intense anxiety enough to frighten the patient. If the patient reports back to the clinician, the clinician may change to a lower dose, e.g., 5 mg instead of 10 mg fluoxetine, or switch to a less activating, more mellow SSRI like citalopram, sertraline, or paroxetine. If patients do not communicate with their clinicians, they will most likely stop taking the offending drug and not return for follow-up. Weight gain from mirtazapine results in discontinuation in many adolescents. Sexual dysfunction from SSRIs or atypical antipsychotics result in discontinuation. One side effect may be destructive to the clinician–patient therapeutic alliance.

Missing doses is a contributing factor in non-adherence, especially when a patient is taking drugs that require multiple dosing through the day, like cyproheptadine, buspirone, and gabapentin. When there are complex dosing schedules for multiple drugs, for example, with an insulin-dependent diabetic adolescent with anxiety and dyspepsia, errors of omission are common.

Fears of addiction and suicide require that the clinician listens carefully to the child and parents to establish a therapeutic alliance and mutual trust before initiating a drug trial. Also, the clinician should be aware of financial issues with a family; some drugs may not be affordable for some families.

Off-Label Prescribing Psychotropic Drugs

Most pediatric gastroenterologists believe that it is sometimes necessary to prescribe drugs that have not been FDA-approved for children. The most common uses and most common drugs and dosing instructions are found in Table 45.2. Detailed explanations and careful communication with the patient and family is essential for adherence and ethical and medicolegal reasons. A typical conversation might start like this: "Amitriptyline is in a class of medicine

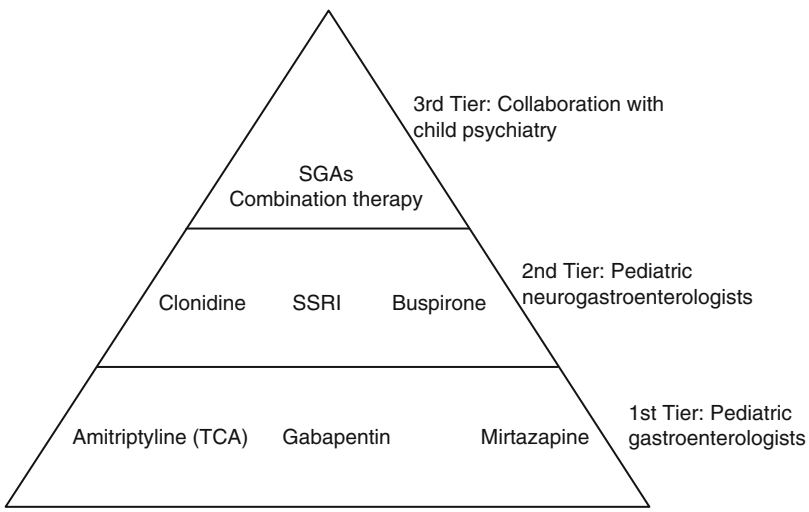

Fig. 45.1 Hierarchy of psychotropic medications in pediatric FGIDs. *SGA* second-generation antipsychotic, *SSRI* selective serotonin reuptake inhibitor, *TCA* tricyclic antidepressant. Adapted from: Hussain S, Hyman P, Psychotropic medications for pediatric functional gastrointestinal disorders. J Pediatr Gastroenterol Nutr 2014;59(3), with permission

called antidepressants, but we are not using amitriptyline for depression. Just a small dose of amitriptyline, about 1/10th the starting dose for depression, is effective treatment for chronic pain. Amitriptyline has been used for close to 40 years for chronic pain. Because it is classified as an antidepressant, the FDA warns us that it may cause a depressed person to think about or even try suicide. Have you ever thought about suicide? If you are not depressed, you are most likely safe, but if you ever have a thought about suicide, please tell me or your parent. Amitriptyline can cause many side effects. Two common ones are sleepiness and constipation. Because it makes you sleepy, we only give it once a day, an hour or two before bedtime. If you get constipated you may need to take another medicine, polyethylene glycol, to keep your stool soft. If you take amitriptyline every day for several months, then forget to take it one night, you may wake up with an upsetting dream. If you do wake with a nightmare, than get up, take your amitriptyline, watch TV for 30 min, then go back to bed. Those are the most common side effects. If you get new symptoms that bother you, please use the email address on my business card to contact me immediately." The prescriber must negotiate a treatment plan, and communicate by telephone or email in the initial days and weeks to assess adherence and involve the patient and family in treatment decisions.

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Electrical Stimulation of the GI Tract

46

Steven Teich

Electrical stimulation of the gastrointestinal tract has been touted as a possible therapy for intestinal motor dysfunction since 1963 when Bilgutay et al. reported the use of transluminal electrical stimulation at the tip of a nasogastric tube to induce peristalsis and shorten the time period of postlaparotomy ileus [1]. They found that stimulation of the stomach with electrical pulse bursts resulted in increased gastric emptying demonstrated by fluoroscopy, but no quantitative measurements were obtained. However, subsequent randomized controlled studies failed to show any benefit of gastric stimulation on decreasing the duration of postoperative ileus [2–4]. In the late 1960s and 1970s, the myoelectrical activity of the gastrointestinal tract was elucidated along with its relationship to gut contractility [5–7]. Out of this initial research, several clinical applications of gastrointestinal electrical stimulation have arisen. These include gastric stimulation for treatment of gastroparesis and sacral nerve stimulation for treatment of urinary disorders and fecal incontinence. All the initial studies and subsequent FDA trials were limited to adult patients. However, over the past 10 years, a few pediatric surgeons interested in pediatric neurogastroenterology have been performing gastric stimulation for gastroparesis and sacral nerve stimulation for fecal and urinary incontinence with excellent results (see below).

46.1 Gastroparesis and Gastric Electrical Stimulation

There are very few pharmacologic agents currently available for the treatment of gastroparesis, and their efficacy in the treatment of severe motility disorders is questionable. At the same time, classic surgical approaches such as pyloroplasty, total gastrectomy, and placement of gastrojejeunal and jejunostomy feeding tubes rarely provide significant, long-term symptom relief in patients with severe gastroparesis. Gastroparesis and severe dyspepsia are associated with poor quality of life, are often refractory to dietary and pharmacological interventions, and are associated with higher medical costs [8, 9].

Gastric electrical stimulation (GES) for the treatment of gastroparesis gained FDA approval with a Humanitarian Device Exemption (<4000 cases diagnosed/year in the United States) in 2000. The Enterra™ therapy system (Medtronic Inc., Minneapolis, MN) requires individual hospital Institutional Review Board approval and should only be implanted after all available medical therapies for gastroparesis have failed. Since 2000 the Enterra™ system has been implanted in more than 10,000 adults worldwide for gastroparesis. Implantation in pediatric patients is more recent with probably <250 children having undergone GES therapy to date [10–12].

GES is a low-energy, high-frequency system that stimulates the nerves that innervate the gastric antral muscle. Several studies have demonstrated that GES improves nausea and vomiting, but the exact mechanisms remain unproven [13–15]. Proposed mechanisms include modulation of enteric or afferent neural activity that influences symptom perception, acceleration of gastric emptying, enhanced vagal activity, alterations in CNS control mechanisms of nausea and vomiting, and enhanced gastric accommodation [14].

Symptomatic improvement is not correlated with improvement in gastric emptying or changes in electrogastrography (EGG) [16]. Patients with drug refractory nausea but baseline normal gastric emptying as well as patients with baseline delayed gastric emptying that does not improve after GES therapy may still experience symptomatic relief [16].

46.1.1 Temporary Gastric Stimulation

Although not part of the FDA-approved protocol, in many patients, temporary GES is used to predict a patient's response to GES [17]. The temporary GES electrode used is

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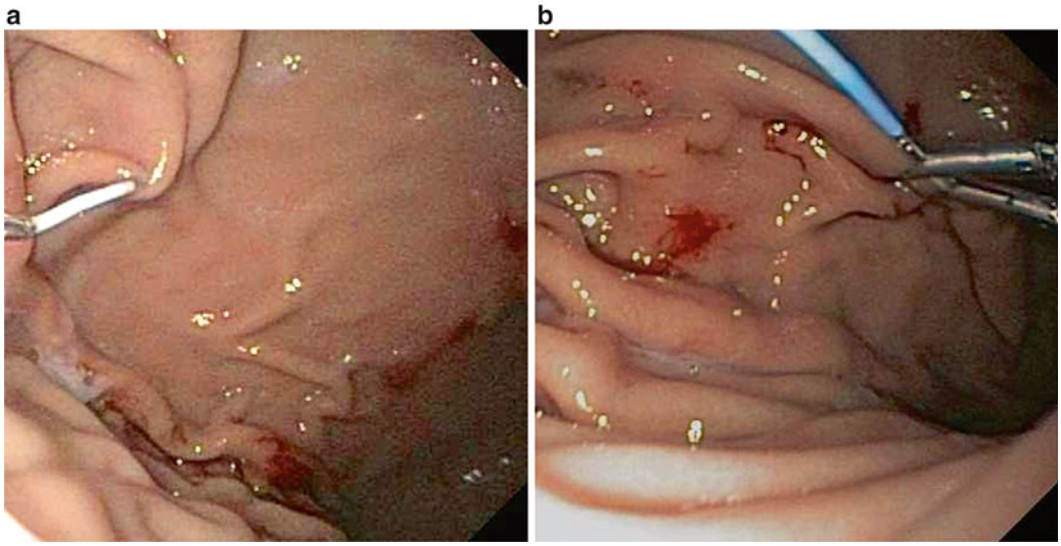

Fig. 46.1 Endoscopic pictures of temporary GES placement. The lead is screwed clockwise into the gastric mucosa (**a**). Clips are placed endoscopically to anchor the lead to the mucosa between the gastric body and antrum (**b**)

a temporary cardiac pacing lead (model 6414-100 or 6414-200, Medtronic Inc., Minneapolis, MN) which is placed through an existing gastrostomy site or passed through the side port of a gastroscope and brought out through the nose or mouth. The lead is screwed clockwise into the gastric mucosa at the junction of the body and antrum of the stomach (Fig. 46.1a). Endoscopic clips are then applied to hold the lead in place (Fig. 46.1b). The lead is connected to an external GES battery that is placed into a telemetry pouch. The pulse generator is interrogated (desired impedance 400–1500 Ω) and initially programmed at relatively high settings (voltage, 5 V; pulse width, 330 μs; frequency, 28 Hz; time on 1.0 s; and time off 4.0 s). This allows the patient response to temporary GES to be determined within 2–3 days. In general the lead can stay in place for about 7 days before eventual dislodgement. The temporary lead is easily removed by rotating counterclockwise with gentle traction.

46.1.2 Permanent Gastric Stimulation

The electrodes for the permanent Enterra™ system can be placed laparoscopically or by open laparotomy if necessary due to previous surgeries or if a gastrostomy is present. Two electrodes 1 cm apart and in parallel alignment are placed intramural along the greater curvature of the stomach at the junction of the antrum and body of the stomach (Fig. 46.2a). The electrodes are placed under endoscopic visualization to ensure that the leads are not intraluminal. The electrodes are then secured to the gastric wall (Fig. 46.2b). The two leads are connected to the GES pulse generator (Fig. 46.2c), and the generator is placed into a subcutaneous pocket (Fig. 46.2d). The pulse generator is interrogated (desired impedance 400–800 Ω) and initially programmed (voltage, 5 V; pulse width, 330 μs; frequency, 14 Hz; time on, 1.0 s; and time off, 4.0 s). Postoperatively, the parameters can be adjusted if the patient does not achieve satisfactory relief of symptoms. However, there is no standard algorithm for modifying the settings. We have had greater success with symptom relief by increasing the pulse width and frequency initially. Adjustments are performed every few weeks to months as needed.

46.1.3 Outcomes

Several studies demonstrate that GES provides long-term relief in adults with gastroparesis. In McCallum's study, there was overall improvement in gastroparesis symptoms and nutritional status and decreased medication usage 56 months after placement of the Enterra™ system [18]. In an earlier study, Lin et al. reported the 1-year postoperative status of 63 adults with gastroparesis who were treated with the Enterra™ system [16]. All symptoms including abdominal pain, bloating/distention, nausea, vomiting, and early satiety were significantly improved. Interestingly, 4-h gastric emptying was not significantly improved. This confirms the observation that symptomatic improvement does not correlate with improvement in gastric emptying.

The first series of pediatric patients with chronic nausea and vomiting successfully treated with GES was reported by Islam et al. [10]. All patients improved initially with temporary gastric stimulation and went on to have implantation of the permanent Enterra™ system [10]. One patient had

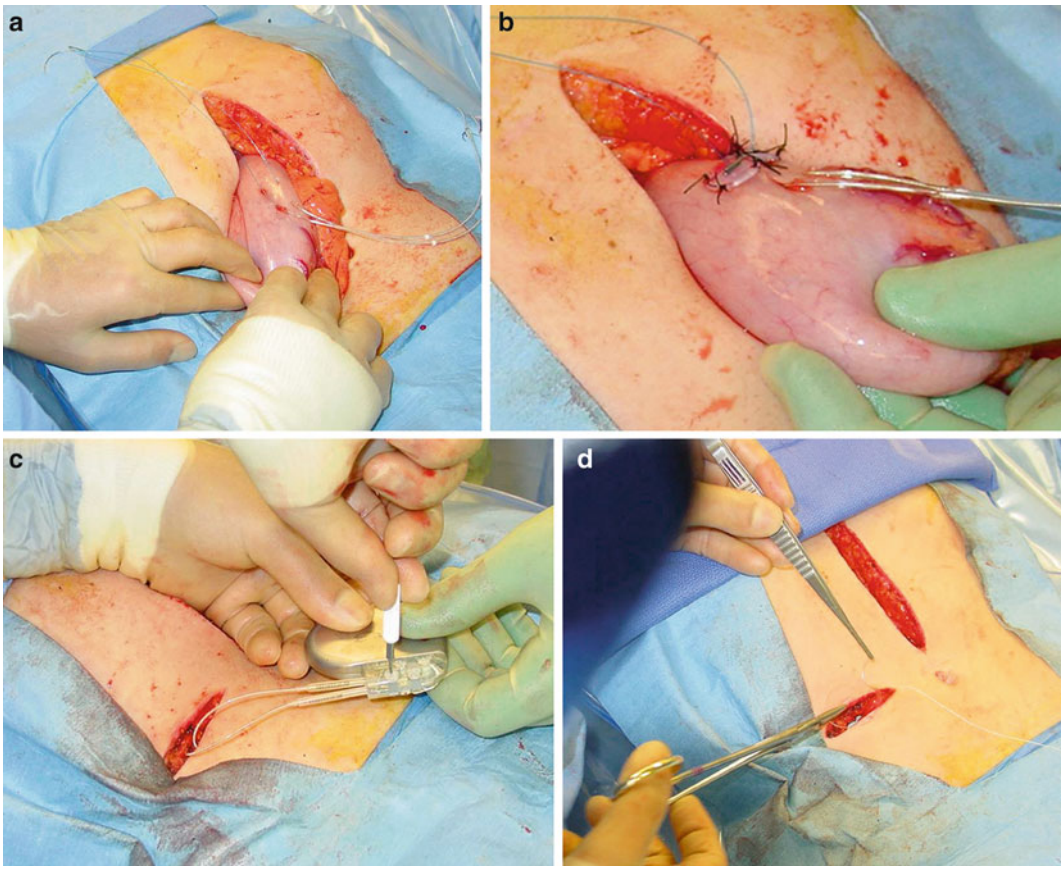

Fig. 46.2 Surgical placement of a GES via laparotomy. Gastric stimulator leads placed parallel to each other in the gastric wall along the greater curvature (**a**). The leads are sutured to the gastric wall (**b**). The leads are attached to the pulse generator (**c**). The pulse generator is sutured into the superficial pocket (**d**)

recurrence of symptoms and one patient required removal of the system. In 2013 we reported our results after placement of the Enterra™ system in our first 16 pediatric patients with chronic nausea and vomiting and functional dyspepsia [11]. After placement of the permanent Enterra™ system, there was significant improvement in severity and frequency of all symptoms. Lu et al. then reported our 2-year follow-up of 24 patients who received GES for functional dyspepsia [12]. There were significant improvements in multiple areas of the PedsQL with 65 % reporting that their health was much improved after placement of the Enterra™ system. Five patients experienced minor complications, but none required removal of the GES system. These initial pediatric series demonstrate excellent results in a difficult group of heterogeneous pediatric patients. In general, pediatric patients with a permanent Enterra™ system are more challenging than adults due to their very active lifestyle that subjects the stimulator leads and battery to potential damage. The effect of significant growth during puberty on the GES system is unknown, as long-term follow-up of pediatric patients with the Enterra™ system has not yet been reported.

There are a few published reports citing the use of GES therapy for treatment of intractable vomiting in patients with chronic intestinal pseudo-obstruction (CIP) [19]. Most likely this is due to the known effect of the Enterra™ system on the stomach with no effect on the small bowel. We have successfully treated several children with CIP-related nausea and vomiting and high-output gastrostomy drainage with the Enterra™ system (unpublished). The GES therapy has allowed the gastrostomy to remain closed and even allowed patients to eat small amounts of food by mouth.

46.2 Sacral Nerve Stimulation

Sacral nerve stimulation is a low-energy, high-frequency system that directly stimulates the third sacral nerve roots. For the urinary system, the effect of sacral nerve stimulation is believed to be somatic afferent inhibition of sensory processing in the spinal cord [20]. For fecal incontinence, sacral nerve stimulation of the pelvic floor via the pelvic plexus and pudendal nerve is thought to excite the autonomic and

somatic nervous systems and cause both direct and reflex-mediated responses to the fecal incontinence mechanism as well as cause changes in cortico-anal excitability [21]. Several studies have documented that sacral nerve stimulation increases anal sphincter resting and squeeze pressure and increases colonic peristalsis with induction of pancolonic propagating waves [22, 23].

In 2012 the FDA approved sacral nerve stimulation as a treatment for fecal incontinence. A study by Tjandra et al. demonstrated that sacral nerve neuromodulation significantly improved the outcome in 60 adult patients with severe fecal incontinence compared with a control group undergoing optimal medical therapy [24]. A prospective multicenter study of 120 adults with fecal incontinence showed significant therapeutic success with 83 % of patients achieving therapeutic success at 12 months and 85 % success at 24 months [25]. Sacral neuromodulation is also cost-effective for urge urinary and/or fecal incontinence [26].

Bowel and bladder dysfunction (BBD) encompasses symptoms of gastrointestinal and urinary dysfunction including chronic constipation, urinary retention, and fecal and urinary incontinence [27]. Adult patients with BBD have been successfully treated with sacral nerve stimulation for more than a decade [24]. However, only in the last 5 years have published reports of pediatric patients with both GI and urinary dysfunction documented impressive results [28–30]. Pediatric patients with BBD represent a complex group of patients that will require long-term follow-up to demonstrate ongoing symptomatic improvement. Since BBD symptoms are difficult to quantify, validated quality of life measures and symptom improvement scoring are essential to determine the clinical utility of sacral nerve stimulation [31–33].

46.2.1 Implantation

The patient is placed in the prone position on the OR table. The sacroiliac joints are identified by fluoroscopy and a line is drawn between them. Starting 2 cm superior and lateral to the midpoint of the line, the access needle is passed through the skin into the third sacral foramen using fluoroscopic guidance to confirm correct positioning. The InterStim™ sacral nerve stimulator system (Medtronic Inc., Minneapolis, MN) stimulator lead is inserted into the third sacral foramen using the Seldinger technique (Fig. 46.3). Placement is confirmed with fluoroscopy and stimulator testing which demonstrates a "bellows effect" of the perineum with dorsiflexion of the toes with stimulation of all four electrodes. The lead is attached to a test stimulator for up to 3 weeks to determine the patient's response to sacral nerve stimulation. If the test is successful, then the test stimulator is removed, and the lead is attached to a permanent sacral nerve stimulator (SNS) pulse generator/battery that is placed into a subcutaneous pocket over the buttock.

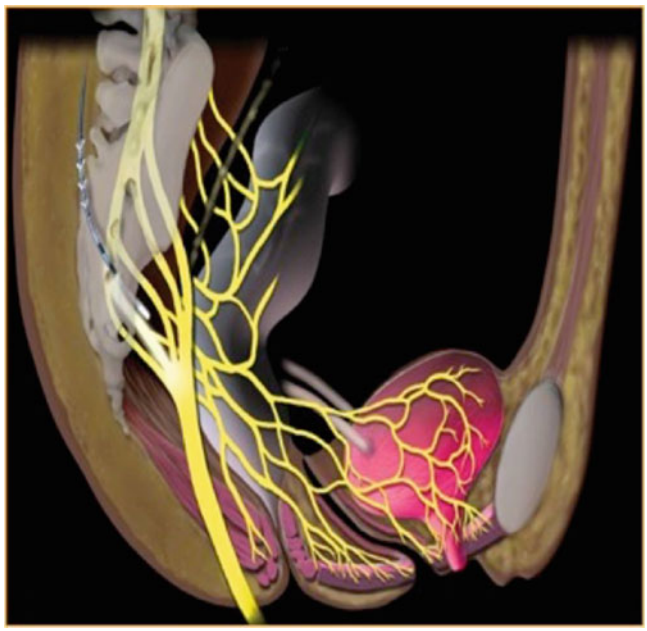

Fig. 46.3 Depiction of sacral nerve stimulator lead in correct position adjacent to L3 nerve root. Reprinted with the permission of Medtronic, Inc. © 2014

46.2.2 Outcomes

In 2014 Dwyer et al. reported on their series of 105 children with BBD. With a median follow-up of 2.72 years, 94 % of patients had improvement of at least one symptom and only 11 % had at least one symptom worsen [30]. Fifty-six percent of patients required reoperation, mainly for device malfunction, and 35 % of patients underwent explantation, mainly for complete symptom resolution. Recently, we reported our results with the first 29 patients with BBD treated with a SNS with a median follow-up of 17.7 months [34]. Fifty-five percent of patients with a pre-SNS cecostomy no longer required an antegrade bowel regimen as they now had voluntary bowel movements, and 91 % of patients no longer require anticholinergic medications for bladder overactivity after sacral nerve stimulation.

As is true with the Enterra™ gastric stimulator system, pediatric patients with a permanent InterStim™ system are more challenging than adults due to their very active lifestyle that subjects the stimulator lead and battery to potential damage. The effect of significant growth during puberty on the SNS system is unknown, as long-term follow-up of pediatric patients with the InterStim™ system has not yet been reported.

46.3 Esophageal Stimulation

Gastroesophageal reflux (GER) caused by transient relaxation of the lower esophageal sphincter commonly occurs in otherwise healthy infants, children, and adults.

Gastroesophageal reflux disease (GERD) is far less common than GER, but the prevalence of GERD in all age groups appears to be increasing [35]. Pediatric patients at high risk for GERD include children with neurologic impairment, esophageal atresia, and some genetic disorders [36, 37]. A fundoplication in these patients is concerning since they are also predisposed to poor esophageal motility, often with swallowing dysfunction. Furthermore, there is a higher risk of gagging and wrap disruption than with otherwise normal patients [38, 39]. For these reasons an alternative to pediatric fundoplication is extremely desirable, especially in these at-risk pediatric subgroups. Over the past 5 years, several adult series utilizing esophageal stimulation rather than fundoplication for GERD have been reported.

The initial studies of electrical stimulation of the lower esophageal sphincter (LES) were performed using a canine model of surgically induced esophagogastric junction incompetence [40–42]. In both acute and chronic models, electrical stimulation of the LES increased resting LES pressure. Human subjects with GERD treated with short-term electrical stimulation of the LES via endoscopically placed temporary electrodes demonstrated similar results with no effect on physiologic LES relaxation [43, 44].

The LES stimulation system (EndoStim BV, the Hague, Netherlands) is an implantable electrical stimulator that delivers long-term electrical stimulation to the LES. The EndoStim™ system is composed of three components: a bipolar electrical stimulator lead, an implantable pulse generator (IPG), and an external programmer. The EndoStim™ system is placed laparoscopically. The two electrodes are implanted within the LES muscle parallel and 1 cm apart (Fig. 46.4a). The electrodes are secured and the lead is attached to the IPG that is placed in a subcutaneous pocket (Fig 46.4b).

Open-label adult human trials are ongoing in Europe, Asia, and South America [45–47]. These studies demonstrated a sustained improvement in GERD outcomes with electrical stimulation therapy of the LES [47]. Patients report sustained improvement in GERD-HRQL, elimination of the need for daily GERD medications, and improvement in esophageal acid exposure [47]. Regurgitation and nocturnal symptoms often remain despite maximal medical therapy and are the major causes of patient dissatisfaction. These two symptoms are tremendously improved with EndoStim™ therapy [47]. A US adult clinical trial has recently been approved by the FDA and should be initiated in 2016. The author is aware that several children with severe GERD outside the United States have been treated with EndoStim™ therapy and pediatric trials outside the United States are in the planning stages.

46.4 Conclusion

While some clinical applications for electrical stimulation of the gastrointestinal tract have been elucidated, much work in the field remains. More controlled trials, especially pediatric ones, are necessary for gastric stimulation, sacral nerve stimulation, and electrical stimulation of the LES. The mechanisms of action for these devices need to be better defined and updated device components and software are necessary. Electrical stimulation of the gastrointestinal tract continues to have great potential for many GI disorders.

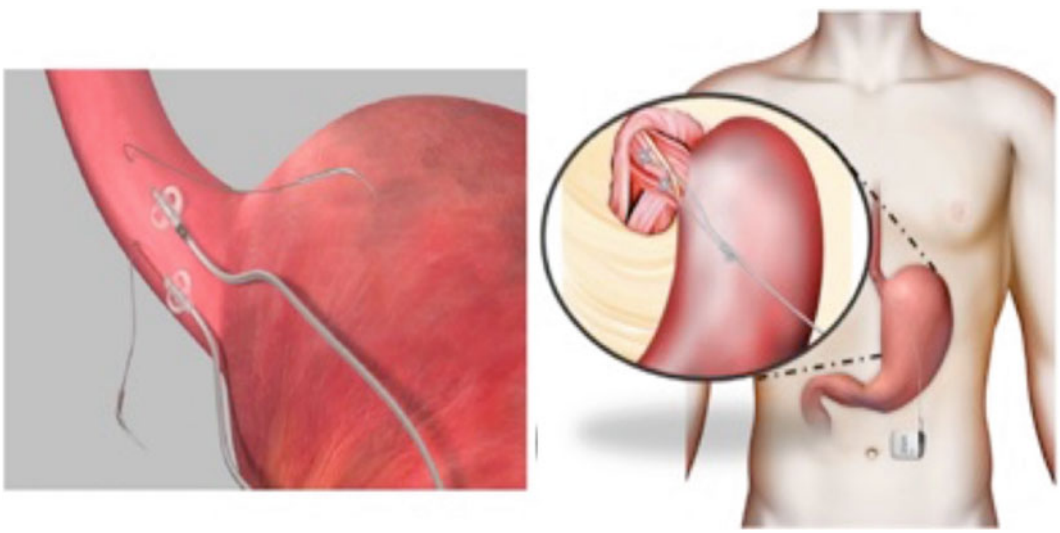

Fig. 46.4 Depiction of lead placement for electrical stimulation of the LES (**a**) and complete system with battery in subcutaneous pocket of the abdominal wall (**b**). Reprinted with the permission of Medtronic, Inc. © 2014

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Cognitive Behavioral Therapy for Functional Gastrointestinal Disorders

47

Miranda A.L. van Tilburg

Symptoms of functional gastrointestinal disorders (FGIDs) are understood to result from dysregulation of the brain–gut axis. Cognitions, emotions, and behaviors play an important role in these disorders by causing, maintaining, or exacerbating symptoms. Recommendations for therapies, therefore, often emphasize the need for integrative care, by combining medical therapies with psychological or behavioral interventions. Among the various psychosocial interventions, cognitive behavioral therapy (CBT) has the widest popularity and largest evidence base for the treatment for FGIDs. Evidence for other treatment modalities, such as hypnosis for the treatment of functional abdominal pain, is growing but not always available to patients since training for therapists nowadays is strongly rooted in CBT techniques. Therefore, this chapter will focus on the application and evidence of CBT.

What Is CBT?

CBT has three basic components, addressing thoughts, emotions, and behaviors (see Fig. 47.1). CBT recognizes that how we *think* can affect how we act and feel, how we *feel* influences our thoughts and behaviors, and how we *behave* influences how we think and feel. In CBT behavioral and cognitive interventions are applied to change all three factors. This makes CBT highly adaptable to various disorders and each patient to maximize therapeutic benefit. This also means that the content of CBT can be very different across therapists, disorders, age range, and other individual or situational characteristics. Many studies allow protocols to be individualized to maximize therapeutic benefit, meaning that even within randomized controlled trials the treatment is often highly variable across subjects.

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The particular therapeutic techniques vary within CBT and include, as the name suggests, both cognitive and behavioral approaches. Cognitive therapy questions and tests cognitions, assumptions, evaluations, and beliefs that might be unhelpful or unrealistic. A child will learn skills on how to recognize these unhelpful cognitions and replace them with more adaptive cognitions. Given that this requires insight into thoughts and verbal fluency to communicate these thoughts with a therapist, CBT is usually recommended for children of school-age or older. However, some components of CBT, especially behavioral therapy, can be applied to children of younger ages. Behavioral techniques include gradually facing activities which may have been avoided; trying out new ways of behaving and reacting, and relaxation exercises such as progressive muscle relaxation, deep-breathing, mindfulness, or guided imagery. Many of these components can also be used as stand-alone therapies, but in that case would not be considered CBT. A third important component of CBT is homework. Skills need to be repeated to be learned and a therapist therefore assigns homework of both cognitive and behavioral components. Lastly, it is important to emphasize that CBT is a time-limited therapy. Session can range from 3 to 12 in children. Unlike psychotherapy or counseling, in which long-term relations are formed between the therapist and client, CBT is brief due to its structured nature and emphasis on teaching children skills that can be used after treatment termination.

Evidence for CBT in FGIDS

CBT is widely used for many FGIDs. However, data is lacking on efficacy of CBT for the majority of these disorders. For example, there is one case study describing CBT for cyclic vomiting syndrome [1], and several case reports of integrative care for rumination including psychological approaches [2, 3]. The most evidence for CBT is in functional constipation and functional abdominal pain disorders, which will be described below.

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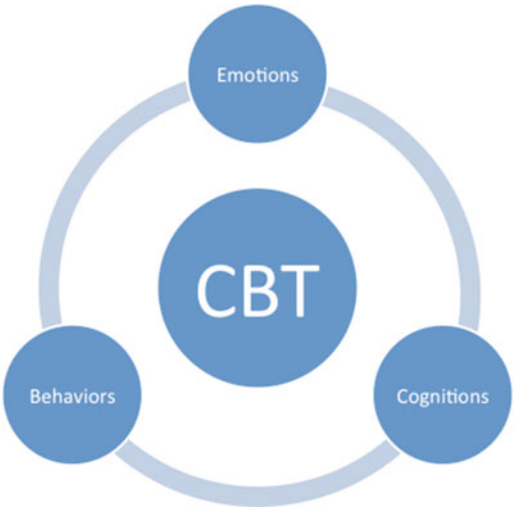

Fig. 47.1 CBT has three basic components, addressing thoughts, emotions, and behaviors

CBT for Functional Constipation

Functional constipation in children is usually a learned behavior [4]. Fear to defecate leads the child to postpone defecation. Retained stool increasingly becomes more painful to defecate, and the child gradually becomes more embarrassed of associated fecal incontinence. This in turn increases fear, stool withholding, and hard stools. Standard medical intervention for functional constipation already involves behavioral elements such as education and daily toilet sitting to address the stool withholding. Medical treatment is associated with 60 % success rate [5]. Given that many children with functional constipation are too young to receive CBT, and parents often have misconceptions of the causes of functional constipation and fecal incontinence, the cognitive element of CBT is often directed at parents, while the behavioral component is directed at the children.

Very few studies have been conducted testing if CBT adds to standard medical-behavioral therapy. A study in 1986 showed no difference between psychotherapy and medical-behavioral therapy, but little information is available about the psychotherapy and children were not randomized to treatment [6]. In a more recent randomized controlled trial similar results were found: the number or treatment responders was not significantly different between those who received CBT (51.5 %) and medical-behavioral treatment (62.3 %) [7]. These authors did find a reduction in the number of children with behavior problems after CBT. For children with fecal incontinence due to constipation there is evidence that Enhanced Toilet Training (ETT) is helpful. ETT includes many behavioral elements such as education, teaching proper defecation skills, reducing fear to defecation, and addressing social isolation and parent–child conflict. Two randomized controlled trials have shown the efficacy of ETT both in person and through internet delivery [8, 9]. Thus, the evidence for CBT in functional constipation is limited although initial evidence suggests it may be effective in reducing fecal incontinence [10].

An additional behavioral treatment in functional constipation is biofeedback. Some evidence has been found for biofeedback for dyssynergic defecation [10], but discussion of biofeedback is outside of the focus of this chapter.

CBT for Functional Abdominal Pain-Related Disorders

Functional Abdominal Pain (FAP) disorders include functional abdominal pain, irritable bowel syndrome, functional dyspepsia, and abdominal migraine. The latter is an uncommon disorder and little data is available on treatment. For FAP disorders the focus of CBT can broadly be divided into being primarily focused on psychological distress (anxiety, depression, stress) or on pain. Many clinicians believe that by reducing anxiety pain may ameliorate [11, 12] since evidence indicates that anxiety is increased in FGIDs [13–17], is associated with increased disability [11], and often precedes FAP [16, 18]. However, anxiety is not associated with maintenance of pain over time [12] and there is lack of evidence that reducing anxiety will reduce symptoms. A meta-analysis reported that psychological therapies for children with chronic pain reduced pain but only had a small effect on emotional functioning [19]. However, this may be because in most CBT for FAP the therapist does not primarily aim to reduce psychological distress but rather focuses on thoughts and coping with pain. The aim is to reduce maladaptive thoughts and coping with and around pain to either decrease symptoms directly or minimize symptom impact on life (e.g., returning back to school). Usually these treatments address understanding of how cognitions and behaviors influence pain experience, cognitive restructuring to challenge negative thoughts that prevent appropriate coping, and coping skills training including relaxation training. Ideally, both parent and child should participate in CBT, as maladaptive response to pain can be reinforced or modeled by parents [20]. Most pain experts agree that a focused approach is needed for FAP [21, 22] although a head-to-head comparison of these two approaches has not yet been done and reducing anxiety can have its own benefits. Where the first approach invites physicians to refer children with anxiety and depression for therapy—and unintentionally reinforce the idea that the pain is “all in the child’s head”—the second approach invites physicians to refer children with poor coping abilities and high disability to a therapist. The latter reinforces the idea that these symptoms can be challenging but their impact is reduced by learning coping skills, an idea that is more acceptable to most families.

Several randomized controlled trials have evaluated the efficacy of CBT for FAP disorders. Most trials compared CBT + standard medical care to standard medical care alone [23–26]. All these studies found significant reductions in pain, and some also in school absences and quality of life. In these trials, children who receive CBT have contact with a therapists for 2–6 sessions, which is not equivalent to the attention and time they receive from their physician, hence it is unknown if effects are due to increased attention by a health care professional or the treatment itself. In one study, CBT was compared to an equivalent number of sessions with the physician [25]; however, it is not clear if children thought the sessions with their physician were helpful. A better approach is to compare CBT to another treatment. This treatment should be the same in time and attention and should have credibility as a treatment for FAP but of lesser efficacy. Humphreys and Gervitz [27] compared CBT to fiber treatment and found more children who were pain free in the first. However, fiber treatment does not control for attention and time. Two studies have used appropriate controls. In a small study by Alfven and Lindstrom [28] ($N = 48$ children) CBT+ physiotherapy was compared to physiotherapy alone. The authors did not report differences in pain. In a large study by Levy and co-authors [29, 30] ($N = 200$) a three session CBT was compared to three session of dietary education. Care was taken that both were equal in time, attention, and credibility. This study added a new aspect to CBT by specifically focusing on parental modeling and reinforcement of pain. Reductions in gastrointestinal symptom severity were observed up to 1 year after treatment [30]. Treatment outcomes were mediated by changes in child coping as well as parental threat of the pain [31], indicating the need to focus CBT on both parent and child. Additional investigations are now underway investigating if CBT delivered to parent alone can impact child's pain and disability. Initial results are promising [32] and the first publications of these results are expected in 2016. Thus, the results of these studies show that there is strong evidence for the use of CBT in FAP disorders.

In addition to CBT, hypnotherapy has gained evidence for treatment of FAP in children [33–37], with large effect sizes. One study also showed some efficacy of written self-disclosure to reduce FAP symptoms [38]. These studies will not be discussed in detail as they are outside of the scope of the current discussion. An interesting new form of CBT, *interoceptive exposure therapy*, has been developed and tested in adults with irritable bowel syndrome [39] and may be of relevance to children as well. This treatment is based on the treatment of bodily sensations in panic disorder. It addresses the fear and avoidance of gut sensations that contribute to pain. Threat of visceral sensations is addressed through cognitive restructuring and interoceptive and in vivo exposure exercises (e.g., wearing tight clothing or eating feared foods). CBT with interoceptive exposure was superior to attention control in reducing bowel symptoms and visceral anxiety [39]. Testing in children is needed before this type of treatment can be recommended.

New Therapeutic Delivery Techniques

CBT is effective in treating FGIDs but not widely available. Only specialized motility centers have psychologists integrated in their clinics [40] and the majority of patients are looking for care in the private sector. There is a lack of therapists trained in FGIDs in private practice, insurance coverage is often insufficient or nonexistent, and most therapists live in highly populated areas restricting access to patients in rural areas. Hence, CBT treatment is not available to the majority of patients. In order to increase care, new types of delivery techniques are being developed. With most households having access to computers or cell phones many therapists have started delivery of therapy through modalities such as Skype. However, each state and country is different in its laws of allowing internet delivery of treatment. There is now some evidence for long-distance therapy.

Palermo and colleagues [41] published a trial of internet delivery of CBT for adolescents with chronic pain and their parents. Internet CBT resulted in significant reductions in activity limitations over internet education but not pain intensity. These results are promising. A trial exclusively in FAP patients is currently being conducted. In addition, a trial of phone delivery of CBT in FAP patients is in progress. Initial results have shown that it is comparable to in-person treatment [29]. van Tilburg and colleagues [33] conducted a trial of audio-delivered guided imagery and found it to be more efficacious in reducing pain than standard medical care. A follow-up study compared audio-therapy at home with hypnotherapy delivered by a therapist and observed that both were comparable [42, 43]. Offering hypnotherapy on audio-discs versus in-person with a therapist saves €4411 per treatment nonresponder. Similar approaches have been tested in studies of children with other types of pain, such as headaches. Delivering CBT through internet, CD-ROM, phone and audiotapes is generally effective in reducing pain [44]. With the advances in technology and wide acceptance of smartphones, we can expect more future internet and app-delivered treatments for FAP. In light of the successful results reported so far, this may alleviate the burden of care and improve access to CBT for all patients with FAP.

Mechanism of CBT

Cognitive behavioral intervention is based on the assumption that changes in cognitions, emotions, and behaviors of both parent and child are responsible for improvement in

FAP; however, these assumptions have not yet been widely tested. The mechanism by which CBT affects pain is still largely unknown. Identifying the active ingredients of treatment is of utmost importance given the variety of CBT approaches. This suggests that there may be active ingredients of therapy that are more important than other techniques in reducing symptoms. For example, guided imagery has been shown to be effective by itself [33, 36] without the addition of other techniques. Below we will discuss the evidence for various purposed mechanism of change.

Changes in Anxiety

As discussed previously, CBT is often delivered to FAP patients in order to reduce anxiety based on the premise that anxiety drives the pain. However, data is lacking to suggest that anxiety changes with CBT and/or is responsible for the changes in pain. A recent meta-analysis suggested there are no changes in anxiety with CBT treatment [45]. Similarly, in a study of CBT among adults with IBS symptoms, changes in psychological distress did not mediate treatment effects [46]. More studies are needed to examine the role of anxiety in pediatric pain and to evaluate if CBT efficacy is driven through reductions in anxiety.

Changes in Coping

CBT for FAP heavily focuses on reducing maladaptive coping with pain in order to reduce symptoms severity and disability. Studies have shown that maladaptive coping, specifically catastrophizing, is common in children with FAP and associated with increased symptoms, depression, anxiety, functional disability, and decreased quality of life [47–52]. Catastrophizing is the tendency to worry about and magnify the threat of pain in combination with feeling helpless to deal with the pain. Catastrophizing is more important than symptom severity in predicting disability [52]. Children with FAP who report high catastrophizing are at increased risk of continued abdominal pain and anxiety into adulthood [53]. In one CBT trial [31], changes in child catastrophizing was a mediator of treatment outcomes, suggesting reduction in catastrophizing is one way in which CBT affects pain and validates to focus on coping with pain.

Parental Reinforcement of Pain Behaviors

Parents play an important role in the way children interpret and cope with symptoms. Most of this evidence comes from children with FAP. Children learn from their parents through modeling and reinforcement [20]. Modeling occurs when a child observes how his/her parent responds to their own symptoms. Is the parent worried or not? Does the parent stop all activities or not? Evidence for modeling comes from studies that show children of parents with IBS report more gastrointestinal symptoms and make more health care visits for these symptoms than children of control parents [54, 55]. Similarly children with functional constipation are more likely to have a parent with constipation than control children [56, 57].

Parents can also unintentionally reinforce symptoms and illness behaviors in their children by expressing support, caring, or concern when the child complains. Although these reactions are a normal part of parenting, too much attention and concern communicates to the child that the symptoms are a threat and normal activities should be stopped. Higher levels of parental attention and solicitousness towards child's pain have been shown to be related to higher levels of pain and disability [55, 58]. Parents tend to act solicitously towards their child when they perceive the pain as more severe [59]. Parental perception of the threat of the child's pain was an important mediator of CBT treatment outcomes [31], indicating the importance of including parents when treating FAP. Likely the same is true for other FGIDs, as children will look to their parents for help and support for any FGID symptom.

Children not only learn from parents how to interpret symptoms, they may also learn efficacious or inefficacious coping skills. Parental catastrophizing impacts child's pain outcomes [60–63] and parents and children are often equally likely to use catastrophizing to cope with pain which suggests a shared tendency for maladaptive coping [61]. Parents who feel distressed and helpless around child's pain are more likely to catastrophize [64]. Parents who catastrophize are also more likely to act protectively and solicitously towards the child when in pain [63]. As discussed above, both coping and parental cognitions have been found to be important mediators of treatment outcomes of CBT in children with FAP [31].

Changes in Central Nervous System

Despite CBT's main focus on psychosocial variables, it has been suggested that it can be accompanied by physiological changes as well, especially in the central nervous system [65]. Brain activation in IBS patients differ from controls in regions associated with emotional arousal, including the anterior cingulate cortex (ACC) and the amygdala [66]. The amygdala is particularly responsive to potential threat of stimuli [67]. Therefore, central nervous system changes may be important mechanisms by which CBT can affect symptoms. Evidence for this was found in a study among adults with IBS. Improvements in symptoms after CBT corresponded with changes in brain activity, particularly in the amygdala and anterior cingulate cortex [46]. In an experimental study, these brain regions

were highly activated when pain threat was ambiguous to IBS patients, indicating the importance of fear of pain in IBS [68]. Other brain regions may possibly also be involved. Fear acquisition or ambiguous threat of pain in IBS patients has been associated with greater activation of the right anterior insula [68, 69], a region that is activated in expectation of abdominal pain. In a case study, Drossman and colleagues [70] followed a young woman with a history of abuse, posttraumatic stress disorder, and functional GI complaints, before and after treatment. Clinical recovery was associated with reduced psychosocial distress, visceral hypersensitivity and changes in the anterior insula, cingulate cortex, and the somatosensory cortex. These findings indicate that changes in brain regions associated with emotional arousal may be a mechanism by which CBT can change FGID symptoms. However, it is not clear if these changes are only descriptive changes of emotional status with CBT versus true mechanisms of change. More data is needed, especially in children, before any definitive conclusions can be drawn.

Furthermore, the role of microbiota and inflammatory system is of wide interest in both FGIDs and mental health and may provide another mechanism for change with CBT. In a study of healthy women, probiotics altered brain regions that control central processing of emotion and sensation [71]. In depressed patients, clinical improvement after CBT corresponds with decreased expression of pro-inflammatory markers [72]. A current study is being conducted to investigate if CBT has an effect on microbial composition of the gut in IBS patients, but data is not yet available. This will be an area of future study and may increase our understanding of the mechanism of pain and CBT.

Conclusions

Changing maladaptive cognitions, behaviors, and feelings is at the heart of CBT therapy and ultimately its success. CBT treatment is an important addition to medical therapy for many FGIDs. Support for efficacy is available for FAP disorders, but studies are largely lacking for other FGIDs. Access to treatment remains an issue as well as and development of long-distance and mobile applications are needed to increase use of CBT. As clinicians become increasingly comfortable with the understanding of the role of the brain–gut axis in the etiology of FGIDs, it is expected that they ultimately will begin to offer CBT delivered in a variety of novel ways much earlier in the treatment paradigm rather than waiting for other comorbid conditions to develop such as anxiety, depression, and impaired function which may lead to a more refractory patient.

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Complementary and Alternative Treatments for Motility and Sensory Disorders

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Arine M. Vlieger and Marc A. Benninga

Complementary and alternative medicine (CAM) is the "diagnosis, treatment, and/or prevention which complements mainstream medicine by contributing to a common whole, by satisfying a demand not met by orthodoxy or by diversifying the conceptual frameworks of medicine" [1] a definition adopted by the Cochrane Collaboration. CAM incorporates many different approaches and methodologies ranging from ancient techniques like acupuncture and Ayurvedic medicine to chiropractics, homeopathy, spiritual healing, and body–mind medicine. CAM has a significant popularity with pediatric gastroenterology patients with a 1-year prevalence of CAM use of 36–41 % [2–4]. Because of this high prevalence and the fact that some complementary therapies are not without adverse effects and may interfere with allopathic medications, it is important for pediatricians and gastroenterologists to become familiar with these therapies. CAM is especially used by children who have low perceived effect of conventional treatment and/or experience significant school absenteeism [4]. Both situations occur frequently in motility and sensory disorders. For example, 30–50 % of the children with functional constipation continue to have severe complaints despite intensive treatment with laxatives [5, 6]. Many patients are therefore dissatisfied with conventional treatment options. Also for pain-related disorders like functional abdominal pain, irritable bowel syndrome, and infantile colic, treatment options have limited efficacy, resulting in dissatisfied patients and parents. Moreover, Youssef et al. showed that adolescents with daily abdominal pain suffer from significant school absenteeism [7]. With the current increasing popularity of CAM in mind, it therefore seems just a matter of time before patients with chronic abdominal pain will consider an alternative route.

Another reason for parents to use CAM is a fear of side effects of allopathic medication, especially in young children. Many CAM therapies are considered "natural" by the general public and thus safer and gentler in some way than the armamentarium of modern medicine. This may explain the high use of CAM in young infants, for example, infants with regurgitation and reflux [4].

In this chapter, we will discuss CAM treatment options for pediatric motility and sensory disorders in which CAM is used fairly often: infantile colic, gastroesophageal reflux, chronic abdominal pain due to functional abdominal pain and irritable bowel syndrome, and constipation. Since CAM treatments may vary widely and research on safety and efficacy of these treatments in children with these disorders is very limited, we will focus on those treatments that have been studied best and/or are being used most, including herbs, acupuncture, homeopathy, hypnotherapy, and manual-based therapies like chiropractics. The use of probiotics is not discussed in this chapter, because this has become mainstream medicine in the last decade.

General Remarks on Safety of CAM Therapies

Many CAM users consider CAM therapies "natural" and equate this with safety. They are often unaware of the fact that many of these therapies have the potential to be directly or indirectly harmful. There are several reports of severe adverse events in children, mostly due to contamination, drug interactions or direct toxic effects of herbs, and dietary supplements (reviewed by Cuzzolin et al. [8]). The problems of toxicity and drug interactions can be extra relevant in young children and infants whose metabolism and organ

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function is immature and less tolerant of even subtle changes in comparison to the adult. To date, only scant data on the frequency of adverse effects of CAM therapies in children are available. A recent review on safety and efficacy of acupuncture in children found a risk of adverse events of 1.55 in 100 treatments [9]. The authors concluded that acupuncture seems to be a safe CAM modality for pediatric patients, although the risk for an individual patient may be hard to determine because certain patients, such as immunosuppressed patients or infants, can be predisposed to an increased risk, and because acupuncturists may differ with respect to their qualifications, skills, and knowledge. Another study determined the frequency of concurrent use of conventional medications and natural health products and their potential interactions in 1800 children [10]. Concurrent use of allopathic drugs and natural products was documented in 20 % of patients with potential interactions in one quarter of them. The authors did not investigate whether these were true interactions resulting in clinical symptoms, but the significant number of children who used both drugs and natural products stresses the importance of studies investigating the safety of natural health products. A meta-analysis on adverse events associated with pediatric spinal manipulation identified 14 cases of direct adverse events involving neurologic or musculoskeletal events [11]. Incidence rates, however, could not be inferred from these observational data. Finally, some words on homeopathy, which is one of the most commonly used CAM treatments in children [12]. Over-the-counter homeopathic remedies are especially popular and used often for common self-limiting conditions. There is little published data on the safety of homeopathy. The few studies, which have been performed on this subject, show that adverse events to homeopathic drugs exist, but are rare and not severe. CAM therapies can also have indirect harmful effects due to missed diagnoses, delaying more effective treatments, and discontinuation of prescribed drugs [13]. These indirect effects are probably not a reason for concern in most motility and sensory disorders, for which conventional treatment options are often limited.

Infantile Colic

Infantile colic is a widespread clinical condition observed in 10–30 % of infants [14]. It occurs mostly in healthy infants and is characterized by paroxysms of excessive, inconsolable crying, frequently accompanied by flushing of the face, drawing-up the legs, meteorism, and flatulence. These crying episodes tend to increase at the age of 6 weeks and usually resolve spontaneously at the end of 3 months. The etiology is not clear, and its limited treatment options frustrate both parents and physicians. It is therefore not surprising that many parents turn toward CAM treatments for their infant.

Acupuncture

Acupuncture has long been used for infantile colic, especially in China, but the published literature is largely restricted to case studies. In 2008, Reinthal et al. investigated the effect of acupuncture in infantile colic in a randomized trial [15]. Forty children with excessive crying unresponsive to conventional therapies were quasi-randomized to control or light needling treatment. Parents were unaware of which group their child was assigned to. Children were given light needling acupuncture on one acupoint (LI4) on both hands for approximately 20 s on four occasions or received the same care except needling. Acupuncture resulted in a significant reduction in the rated crying intensity, and also pain-related behavior, like facial expression, was significantly less pronounced in the light needling group. The results of this study are interesting but need to be confirmed in larger, double-blind controlled trials.

Homeopathy

Homeopathic treatments, especially over-the-counter remedies, are very often used in infants with colic [12, 16], but data on its efficacy are lacking. One observational cohort study in 204 children compared the effect of a standard homeopathic preparation with a conventional drug (scopolamine) in the treatment of abdominal cramps. The analysis showed comparative improvements with both treatments in spasms, pain, sleeping disturbances, and crying. However, no double-blind RCT has been performed with this homeopathic preparation to confirm these findings, so the effect of this homeopathic product in the treatment of infantile colic is still unknown [17].

Manual-Based Treatments

One of the most frequently used treatments for infantile colic is spinal manipulation, given by chiropractors, manual therapists, osteopaths, or craniosacral therapists. It is often claimed by therapists that spinal manipulation is an effective treatment for colic. However, a systematic review in 2009 of three randomized clinical trials showed that the methodological quality of these trials was low with very low sample sizes and insufficient control of placebo effects [18]. It was concluded that to date there is no good evidence showing that spinal manipulation is effective for infantile colic. Moreover, the recent reported fatal adverse reaction on a 3-month-old baby upon craniosacral therapy demonstrates that spinal manipulation is not without risks and therefore should not be recommended for infantile colic [19].

Gastroesophageal Reflux

Gastroesophageal reflux (GER) is defined as the passive flow of gastric contents into the esophagus. It is important to recognize that GER is a normal physiologic phenomenon and therefore occurs to some extent in all infants and children. Symptoms, especially regurgitation, are very common in infancy and are reported by parents to occur at least regularly in 70 % of 4-month-old babies [20].

Regurgitation and vomiting are the most typical symptoms related to GER [21]. However, most of the infants experiencing those symptoms are not considered to have GER disease. A combination of regurgitation and/or vomiting with excessive crying and feed-related irritability is most suggestive of GER disease in infants. Other symptoms such as hematemesis and failure to thrive are indicative of severe disease. Of the many extraesophageal symptoms such as apparent life-threatening events, laryngitis, hoarseness, and asthma, only dental erosions and Sandifer's syndrome are convincingly shown to be GER related [22].

Parental education, guidance, and support are usually sufficient to manage healthy, thriving infants with symptoms likely to be secondary to physiologic GER. If symptoms persist despite these conservative measures, it can be helpful to eliminate cow milk from the infant's diet (or in case of breastfeeding, from the mother's diet). Therefore, formula-fed infants with recurrent vomiting may benefit from a 2- to 4-week trial of an extensively hydrolyzed protein formula [23]. Thickening feeds has been shown to decrease the frequency of regurgitation but not other symptoms and does not decrease acid exposure [24]. Many studies have been performed looking at the effect of posture in the postprandial position. Although some studies suggest a beneficial effect of lifting the head of the cot, there is not enough evidence to support this in clinical practice [24]. Compared to supine position, prone position significantly reduces the number of acid GER episodes but increases the risk for sudden infant death syndrome (SIDS) [25, 26]. The major pharmacologic agents currently used for treating GERD in children are gastric acid-buffering agents, mucosal surface barriers, and gastric antisecretory agents.

Although many of the simple therapeutic interventions are helpful in infants and children with GER, 40 % of the parents still seek help in the complementary medicine circuit. Despite this high percentage, no well-designed trials exist which evaluate the efficacy of the complementary treatments that are used by parents for this disorder, such as osteopathy or naturopathy. Therefore, this review will only focus on acupuncture with respect to GERD.

Acupuncture

Transient lower esophageal sphincter relaxations (TLESR) have been shown to underlie most GER episodes in healthy volunteers and healthy premature infants as well as in adult and pediatric patients with GER disease [27]. Current data indicate that transient LES relaxations are mediated via a vago-vagal pathway initiated by tension receptors located in the proximal stomach musculature [28].

The mechanism by which acupuncture improves GERD-related symptoms remains to be elucidated. It has been shown that electric acupuncture at zusanli (ST-36) can increase the basal LES pressure, whereas transcutaneous electric nerve stimulation (TENS) at Hukou acupoint increases the degree of LES relaxation in volunteers [29]. Others have suggested that TENS at neiguan may inhibit the rate of TLESRs triggered by gastric distention and reduce the perception to gastric distention in human beings [30, 31]. A recent study in 12 healthy cats showed that electric acupoint stimulation at neiguan significantly inhibits the frequency of TLESR [32]. This effect appears to act on the brain stem and may be mediated through nitric oxide, CCK-A receptor, and mu-opioid receptors.

A randomized parallel group trial studied 30 adult patients (age > 18 years) with a 3-month history of GERD-related symptoms at least 2 days per week while taking standard-dose omeprazole 20 mg once daily [33]. The acupuncture protocol consisted of five acupuncture points according to the traditional Chinese medicine pattern diagnosis. The treatment consisted of ten acupuncture sessions (25 min each) over 4 weeks. Acupuncture resulted in a significant improvement in daytime heartburn, nighttime heartburn, and acid regurgitation when compared with doubling the PPI dose. A limitation of the study was the small sample size and the lack of a sham acupuncture arm. The authors point out, however, that increasing recognition in the acupuncture literature exists that superficial (needling of the skin), sham (needling of non-acupuncture points), and placebo (needling with blunt tip that does not penetrate the skin) acupuncture also provide an active therapeutic effect [34]. No such studies have been performed in either infants or children with gastroesophageal reflux disease.

Functional Abdominal Pain and Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) and functional abdominal pain (FAP) in childhood are pediatric functional gastrointestinal disorders, which are characterized by chronic or recurrent

abdominal pain, and no evidence of an underlying organic disorder. By definition, altered bowel movements and/or relief of pain after defecation are seen in IBS, while defecation pattern is normal in patients with FAP [35]. IBS and FAP are among the most common pain complaints in childhood with reported prevalence's between 0.3 and 19 % [36]. Quality of life scores of IBS and FAP children are significantly reduced, and many children also suffer from anxiety and/or depression, highlighting the clinical significance [7, 37]. Standard medical treatment is symptomatic and consists of dietary advice, education, and/or pain medication. Sometimes patients are referred to a child psychologist for behavioral therapy. All these interventions may result in reduction of symptoms, but many children continue to experience symptoms for years, even into adulthood. It is therefore not surprising that a significant number of patients consider alternative treatments. Given the high placebo response shown in IBS studies, it is expected that many patients will experience at least a short-term benefit of any of these treatments.

Acupuncture

A 2006 Cochrane Database article reviewed six randomized trials using acupuncture in IBS [38]. It was concluded that the trials were generally of poor quality, included relatively small numbers of patients, and differed significantly in the acupuncture method utilized. The review found inconclusive evidence as to whether acupuncture is superior to sham acupuncture in IBS. Subsequently, two studies with a total of 273 patients were published comparing real acupuncture to sham acupuncture or a waiting list. In both studies no significant difference was found between the response rates in patients receiving acupuncture and sham acupuncture on global improvement of IBS, although patients in both groups improved significantly compared to baseline [39, 40]. These results suggest that acupuncture has a potential role in the treatment of IBS, but its effect might be nonspecific. However, Schneider et al. recently showed that real acupuncture in comparison to sham acupuncture had more specific physiological effects with a more pronounced decrease in salivary cortisol and an increased parasympathetic tone [41]. They concluded that different mechanisms seem to be involved in sham and real acupuncture-driven improvements, but the specific mode of action of acupuncture in IBS remains unclear and deserves further evaluation. Whether acupuncture is also effective in the treatment of children with IBS or FAP is unknown, since trials in this patient group are lacking. Awaiting such trials, physicians might already consider acupuncture as a potential treatment option in children with refractory IBS or FAP, since acupuncture is considered a safe CAM modality for pediatric patients [9].

Herbs

Herbals and botanicals have been used for hundreds of years for abdominal complaints in both adults and children, but good scientific evidence of their effectiveness is sparse. Two of three randomized controlled trials (RCTs) demonstrated that (Chinese) herbal medicine may offer improvement in some adults with irritable bowel syndrome (IBS), and a superior posttreatment effect was found with individualized formulations in comparison to standardized preparations [42–44]. No studies have been performed in children. Peppermint, which is commonly found in over-the-counter preparations for IBS, has also been found effective [45]. The mechanism of action is thought to be from the menthol component of peppermint that relaxes gastrointestinal smooth muscle by blocking calcium channels [46]. In children with IBS, the use of peppermint oil seems to be both safe and beneficial: in a small randomized, double-blind controlled 2-week trial, 76 % of the patients receiving enteric-coated peppermint oil capsules reported a decrease in symptom severity versus only 19 % in the placebo group [47]. Another popular herb in IBS is ginger (*Zingiber officinale*), especially used by patients with nausea and dyspepsia as one of the main complaints [48]. It has a prokinetic action probably mediated by spasmolytic constituents of the calcium antagonist type [49]. Ginger has been proven effective for reducing postoperative nausea and vomiting [50] and nausea in early pregnancy [51]. It seems to be relatively safe, although abdominal discomfort has been noted in some patients. NO RCTs have been performed in children with IBS, FAP, or functional dyspepsia.

Hypnotherapy

Brain–gut interactions are increasingly recognized in the pathogenesis of IBS and FAP, making body–mind medicine an appealing therapeutic approach. A body–mind technique that seems to be very useful in the treatment of children with FAP and IBS is gut-directed hypnotherapy. In this therapy a hypnotic trance is induced in which patients are given suggestions, directed toward control and normalization of gut function in addition to relevant ego-strengthening interventions. There is fairly strong evidence supporting the use of this CAM modality. A Cochrane review in 2006 found four RCTs in adults. The therapeutic effect of hypnotherapy was found to be superior to that of a waiting list control or usual medical management for abdominal pain and composite primary IBS symptoms [52]. Data were not pooled for meta-analysis due to differences in outcome measures and study design. One subsequent trial in children with FAP and IBS showed that developmentally appropriate gut-directed

hypnotherapy was highly superior compared to standard medical care with complete remission of symptoms in 85 % of children at 1-year follow-up versus 25 % in the control group [53]. In an intriguing recent study, hypnotherapy based on self-exercises at home with the help of recorded scripts on CDs was used in a group of children with functional abdominal pain [54]. The CDs contained similar exercises as used in individual hypnotherapy. About two thirds responded favorably to this therapy compared to only 27 % in the control group. Audio-recorded self-hypnosis can become an attractive first-line therapy for children with FAP or IBS because of its low costs and direct availability, but further studies are needed to compare its effectiveness with individual hypnotherapy given by a therapist.

Manual-Based Therapies

Not many studies have been performed with manual-based therapies in patients with FAP or IBS. In adults with IBS, a small single-blind trial did not show any benefit of reflexology foot massage on abdominal pain, defecation frequency, and abdominal distension [55]. A pilot study with 39 adult IBS patients investigated the effect of osteopathy, a manual treatment which relies on mobilizing and manipulating procedures in order to relieve complaints [56]. Compared to standard medical treatment, osteopathy resulted in a significantly lower disease severity index scores and a higher percentage of patients with definite overall improvement. It was concluded that osteopathic therapy might be a promising alternative in the treatment of patients with IBS. However, more studies are needed to confirm these findings before osteopathy can be advocated as a treatment option for IBS/FAP.

Constipation

The diagnosis of functional constipation in infants and children is based on a complex of symptoms in the absence of an underlying organic cause. These children often have infrequent, painful, large, and hard bowel movements in combination with fecal incontinence. Furthermore, many of these children tend to show withholding behavior [35]. A recent systematic review reported that the worldwide prevalence of childhood constipation in the general population ranges from 0.7 to 29.6 % [57]. As in children with functional abdominal pain, chronic symptoms of functional constipation are associated with a lower quality of life, as measured with generic questionnaires [58]. Parents reported even lower quality of life than their children which was probably impacted by the duration of their child's symptoms and by family members having similar symptoms [58]. The backbone for treatment of functional constipation consists of education of the child and parents, behavioral modifications, and laxative therapy [59]. Once disimpaction is accomplished, maintenance therapy is essential to prevent re-accumulation of feces. Daily oral laxative therapy needs to be continued for 3 months or longer at a dose that produces a daily soft stool without side effects. In many children, symptoms of constipation will resolve within this period. However, persistence of symptoms is reported in 30–52 % of children in studies with at least 5 years of follow-up [60]. Not surprisingly Vlieger et al. showed that 36 % of patients with constipation visiting a gastroenterology outpatient clinic used a least ≥ CAM modality [4].

This review will discuss the effects of acupuncture, herbal therapies, reflexology, and body massage in the treatment of pediatric functional constipation. Since no well-designed studies could be identified on the effect of hypnotherapy, homeopathy, chiropractic and osteopathic manipulation, and energy therapies such as Reiki and healing touch, these topics will not be discussed here.

Acupuncture

Little effort has been made to investigate the efficacy of acupuncture on constipation. A recently published review identified a total of 29 clinical studies evaluating the complementary effects of auriculotherapy as treatment option for constipation. However, generalization of these findings is limited because of two significant methodological flaws: (1) uncertainty in accurate acupoints identification and subjects' compliance to instructions resulted in varied doses of intervention received and (2) inconsistent intervention protocols and therapeutic outcome criteria make comparison among different studies difficult [61, 62].

Acupuncture can accelerate the release of opioid peptides in the central nervous system, but its effect on opioid activity and constipation is not known. Investigators in one study in children with chronic constipation looked at the effect of acupuncture on symptoms and on basal plasma panopioid levels—the ratio of plasma binding to opioid receptors in the brain [63]. The study regimen consisted of 5 weekly placebo acupuncture sessions followed by 10 weekly true acupuncture sessions. A significant increase in frequency of bowel movements occurred in both boys and girls (1.5–4.4/week and 1.4–5.6/week, respectively, each $P < 0.01$) after treatment. The panopioid activity was lower in the control children and increased only in the children who received the true acupuncture sessions. Out of 27 children who started, 10 did not complete the study due to poor compliance. In contrast to the study in children, a study of acupuncture performed in adults with chronic constipation did not show any improvement in symptoms [64].

Herbs

Herbals and botanicals, and especially traditional Chinese medicine, have been used in many cultures over thousands of years for defecation disorders in both children and adults. Although there are many Chinese herbal medicine (CHM) interventions available, and some have been verified by clinical trials, their efficacy and safety are still questioned by both patients and health-care providers worldwide. A 2009 systematic review of the literature identified a total of 62 articles of which 35 were reviewed including a total of 3, 571 patients (ranging in age from 1 month to 93 years) [65]. Although the authors conclude that the results of the different studies included and favored the tested CHM interventions in comparison with controls, the results of these trials should be interpreted with caution due to the generally low methodological quality of the included studies. First, all studies provided insufficient information on how the random allocation was generated and/or concealed, which is necessary to avoid selection bias. Second, none of the studies used any blinding method. Third, none of the included studies addressed incomplete outcome data, such as missing data due to attrition or exclusions. Fourth, none of the studies had been registered, and finally the majority of experimental CHM interventions were prepared by the investigators without detailed information describing underlying rationales on formulation, dosage, manufacturing process, etc.

A recent observational study investigated the use of a Japanese herbal medicine, Dai-Kenchu-To (DKT), composed of three herbs, zanthoxylum fruit, ginseng root, and dried ginger rhizomes, in ten children with non-defined severe constipation over a 3- to 12-month period [66]. In this small study, the authors conclude that DKT had a favorable clinical effect on symptoms of constipation in children such as fecal incontinence. No data were, however, provided about the effect on defecation frequency, consistency of stools, and abdominal pain.

Historically, the botanical agents *Rhamnus purshiana* and *Senna* (Sannae folum) have been used as stimulant laxatives and are approved by the Food and Drug Administration for the treatment of constipation in children over 2 years of age (NICE guideline); however, studies evaluating safety and efficacy of these stimulants are lacking.

Reflexology

Reflexology is based on the notion that different areas on the hands and feet correspond to glands, organs, and other parts of the body and that pressure on those specific areas can have therapeutic effect. The mechanism underlying this treatment is unknown, but many believe that the effect is caused by an improvement of blood flow that encourages relaxation and the healing response [67]. The effect of reflexology has also been studied in 50 children, ages 3–14 years, with constipation and fecal incontinence [68]. After 6 weekly reflexology sessions of 30 min, results supported an increase in frequency of bowel movements and a decrease in fecal incontinence episodes with only 2 % instead of 36 % of the study children having fewer than one bowel movement a week during treatment. No side effects were reported, but double-blind studies with longer follow-up are needed to exclude placebo effect and determine the long-term outcome of this treatment.

Massage

Abdominal massage for the relief of constipation was a commonly practiced therapy in India, China, Arabia, Egypt, and Greece, but its use declined over time. As for other complementary therapies, there is now a resurgence of interest in the role that abdominal massage may play in relieving constipation, although preliminary studies have been disappointing although many patients perceived the therapy as agreeable [69].

Conclusion

Some CAM therapies and especially acupuncture and hypnotherapy show considerable promise in the treatment of children with motility and sensory disorders. Since so many patients are using CAM and because some of these modalities are not always devoid of risks, it is important for pediatricians and pediatric gastroenterologists to be familiar with these therapies. Moreover, given the ongoing interest in CAM by pediatric patients, it is in the public interest to establish more rigorous evidence on efficacy and safety of these therapies. Only this way, we can head toward integration of evidence-based CAM modalities into pediatric motility and sensory disorders. Until then, one should try to recognize both possibilities and limitations of CAM therapies in discussing these treatment options with parents and patients.

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Cellular-Based Therapies for Paediatric GI Motility Disorders

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Currently the therapeutic options for many gastrointestinal (GI) motility conditions, especially the most severe, remain woefully inadequate. For these disorders, treatments are limited to palliative interventions such as surgery and the provision of artificial nutrition. This highlights the fact that current treatments aim to prevent the mortality and limit morbidity associated with the most significant complications of the diseases but are not designed to be curative.

Although it is clear that both surgery and parenteral nutrition (PN) have revolutionised the management and overall survival of children suffering from severe intestinal motility disorders, most of whom would otherwise not have survived beyond the neonatal period [1–3], these conditions continue to be associated with high levels of morbidity and mortality. Mortality rates still remain in the order of 8–20 % and mostly relate to iatrogenic complications of central venous catheter-related sepsis and PN-related liver failure [1–6].

The poor outcome of gut motility disorders is perhaps best exemplified by Hirschsprung's disease (HSCR) where despite substantial surgical expertise and relatively rare use of PN, the post-operative morbidity data is compelling [7–12]. A long-term follow-up study of 48 HSCR patients with total colonic aganglionosis (TCA) by Tsuji et al. showed that 94 % survived. Among the survivors, faecal incontinence was present in 82 % of patients at 5 years, 57 % at 10 years and 33 % at 15 years follow-up. On anthropometric follow-up, 63 % of patients with TCA were failing to thrive at 15 years [7]. These findings are supported by a recent systematic review [12]. Other studies suggest that such problems occur irrespective of the extent of aganglionosis [8] and persist in more than 50 % of HSCR patients into early adulthood [9].

Such data highlights the need for improved, more curative, therapies for gut motility disorders, including those designed to definitively restore missing components or rescue dysfunctional ones. With particular attention to enteric neuropathies, this chapter summarises the tremendous progress that has been made, and the challenges that remain, in the development of new curative cellular therapies for gut motility disorders.

Stem Cell Therapies for ENS Disorders: Background and Concepts

Recent advances in molecular biology and genetics have significantly enhanced our understanding of the development and function of the gut neuromusculature, especially its intrinsic innervation, the enteric nervous system (ENS). This has not only facilitated our appreciation of the pathogenesis of gut motility disorders but has also allowed the identification of novel tools and targets for therapy [13, 14]. Stem cells, defined by their unique ability to self-renew, proliferate extensively and differentiate into multiple lineages, provide one such tool. For the purposes of this review, the term 'stem cell' has been used to denote both progenitor cells, with limited self-renewal and differentiation capacities, and stem cells in the truest sense.

Successful stem cell therapy has already been performed for many years in the form of bone marrow transplants, and there is currently enormous interest in the potential of stem cell therapy to treat diseases of both the central nervous system (CNS) [15] and ENS [16–18]. Compared with other systems, the use of stem cell therapy for treating diseases of the ENS has some potential advantages including accessibility to source and deliver cells, as well as the possibility of autologous transplantation.

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Sourcing Stem Cells for ENS Therapy

In the quest to develop cellular therapies for ENS disorders, a number of tissue sources have been explored to identify a cell type capable of generating ENS components upon transplantation. These are discussed below and summarised in Table 49.1.

Embryonic stem (ES) cells derived from the inner cell mass of the blastocyst are pluripotent and capable of giving rise to all the cell types in the body [45]. Their initial discovery [46, 47] and subsequent isolation from human embryos [48] led to significant interest for their use in regenerative medicine, especially given their potential to generate 'unlimited' quantities of cells for replacement therapies. ES cells

Table 49.1 Possible sources of stem cells to generate a putative ENS

Source	Selection/ propagation	Recipient or host tissue	Differentiation in host tissue	Function	References
PSC (ES/iPS)					
Mouse ES cells	EB	Mouse renal capsule	N, M, ICC and EP	Regular slow wave activity and spontaneous spike potentials	[19–22]
Mouse ES cells	Sox10	Aneural hindgut explant from mouse embryo in vitro	N	ND	[23]
Human PSC	SOX10, CD49D	Colon of Ednrb−/− mouse	N+G	Prolonged survival of mice with HSCR	[24]
CNS					
Embryonic mouse brain	NS	nNOS−/− mice stomach in vivo	N+G	Improved gastric function	[25, 26]
Embryonic rat brain	NS	Chemically denervated rat rectum in vivo	N+G	Restored rectoanal inhibitory reflex	[27]
Embryonic rat neural tube	NS	Chemically denervated rat colon in vivo	N+G	Improved colonic motility	[28]
Neural crest ENS					
Embryonic mouse gut	Sorted Ret+ cells	Aganglionic gut explant from Ret−/− mouse embryo in vitro	N+G	ND	[29, 30]
Embryonic/postnatal mouse gut	NS	Aganglionic gut explant from Ret−/− mouse embryo in vitro	N+G	ND	[31]
Postnatal/adult rat gut	Sorted p75+/α4 integrin+ cells	Aganglionic gut explant from Ednrb−/− mouse embryo grown on chorioallantoic membrane of chick embryos	N	ND	[32–34]
Embryonic rat gut	Sorted p75+/α4 integrin+ cells	Ednrbsl/sl rat bowel in vivo, i.p.	N+G	ND	[35]
Embryonic/postnatal human gut	NS	Human gut explant in vitro	N	ND	[36]
HSCR patient gut	NS	Aneural hindgut explant from mouse embryo in vitro	N+G+ICC	Restored motility patterns to hindgut	[37, 38]
Postnatal human gut mucosa	NS	Explant from aganglionic region of HSCR patient in vitro	N	ND	[39]
ENS cell line from immortomice	Sorted p75+ cells	Piebald or nNOS−/− mice colon in vivo	N	Improved colonic motility	[40]
Embryonic mouse gut	Sox2	Aneural hindgut explant from mouse embryo in vitro	N	ND	[41]
Postnatal mouse gut	Sorted ENCCs (Wnt1-Cre/YFP mice)	Wild-type mouse colon in vivo	N+G	Functional integration with host neurons by Ca2+ imaging	[42]
	Sorted ENCCs (*EdnrbKik* mice)	Wild-type mouse colon in vivo	N+G	Functioning neurons by intracellular recording	[43]
Other NCCs					
Embryonic mouse neural tube	Neural tube explant	Dom/+ mouse colon in vivo, i.p.	N+G	ND	[44]
Embryonic rat peripheral nerve	Sorted p75+/α4 integrin+ cells	Into migratory pathway of embryonic chickens in ovo	Gut; no, peripheral nerve; N+G	ND	[32, 33]

CNS central nervous system, *EB* embryoid body, *ENCCs* enteric neural crest cells, *ENS* enteric nervous system, *EP* epithelium, *ES* embryonic stem (cells), *G* glial cells, *HSCR* Hirschsprung's disease, *ICC* interstitial cells of Cajal, *i.p.* intraperitoneally, *iPS* induced pluripotent stem (cells), *M* myofibroblasts, *N* neuron, *NCCs* neural crest cells, *ND* not determined, *NS* neurospheres, *PSC* pluripotent stem cells

from both mouse (mES) and human (hES) are capable of producing a range of neural cell types [49–55], including enteric neurons [23, 56, 57]. Kawaguchi et al. demonstrated that neural crest (NC) progenitors (Sox10 expressing)) derived from mES cells can colonise and give rise to neurons (Hu and TuJ1 expressing) within explants of aneural hindgut of mouse embryos [23]. Neural progenitors derived from hES cells also appear capable of generating NC-like cells that migrate along normal NC migratory pathways in quail embryos in vivo and colonise explants of embryonic mouse gut in vitro where they give rise to neurons [56, 58].

Apart from neurons, mES cells also appear capable of generating 'gut-like' structures [19–21, 59–62]. These structures are 0.2–1.5 mm in diameter and contain an endodermal epithelium, intestinal epithelial stem cells, a layer of smooth muscle cells and interstitial cells of Cajal (ICCs); they also exhibit spontaneous contractions [19–21, 59–62]. Although they show some similarities to normal gut organogenesis [21], the requirement for brain-derived neurotrophic factor (BDNF) for neuron development differs from normal enteric neuron development, which does not require BDNF [63]. It is still unclear whether gut-like structures derived from ES cells will be useful for cell therapy, whereas generation of functioning gut epithelial tissue in vitro will provide a platform to study a wide spectrum of GI research. It has been shown that these 'organoids' can be manipulated to mimic human GI diseases, including Menetrier disease; hence they can be used as disease models [62].

CNS-Derived Stem Cells

Although it had long been believed that the CNS in mammals is incapable of regenerating after birth, adult neurogenesis is now well established, including in humans [64–70]. This neurogenesis appears to be affected by a population of self-renewing, multipotent progenitors known as neural stem cells (NSCs) [71, 72]. CNS–NSCs were one of the first cell types tested for ENS therapy as several features were thought to make them suitable [17]. Transplanting CNS–NSCs into the pyloric wall of an animal model of gastroparesis (nNOS−/− mice), Micci et al. showed that these cells predominantly gave rise to neuronal nitric oxide synthase (nNOS) expressing neurons, which resulted in significant improvements in gastric emptying and in electric field stimulation-induced relaxation [25]. Although the mechanisms underlying such improvement of gastric function were unclear, the study provided the first demonstration that NSCs transplanted into the bowel were able to ameliorate a motility disorder [16]. More recently, transplantation of foetal cerebral cortex-derived CNS–NSCs into the rectum of adult rats, where enteric neurons had been destroyed chemically, resulted in the generation of neurons and glial cells, an increase in both the expression of nNOS and choline acetyltransferase (ChAT) and restoration of the rectoanal inhibitory reflex [27].

Cells isolated from the mid-embryonic rat neural tube or 'neuroepithelial stem cells' have also been shown to give rise to enteric neurons in vivo in experimental animals similar to that described above [28, 73]. Transplantation of these cells appeared to result in nNOS- and ChAT-expressing neurons and improvements in colonic motility in recipient colons in which the ENS had been chemically destroyed [28, 73].

Neural Crest Stem Cells

Perhaps the most attractive tools for ENS therapy are derivatives of those neural crest (NC) cells that initially gave rise to the ENS itself. This phenomenon is described in detail in earlier chapters. Briefly, during embryogenesis NC cells emigrate from the NC, a transient structure that forms at the dorsolateral surface of the developing neural tube, and migrate along defined pathways to give rise to diverse structures including the ENS [74, 75]. Vagal (hindbrain) NC cells arising adjacent to somites 1–7 [76, 77] enter the foregut and migrate along the developing gastrointestinal tract to give rise to the majority of the ENS [78–80]. The capacity to rescue the ENS appears to be limited to NC cells fated to give rise to the ENS itself [32], and although there is some data to suggest that vagal NC have some therapeutic potential [44], the most promising avenue appears to be the use of NC derivatives isolated from the gut.

Enteric Neural Crest Stem Cells (ENS Stem Cells)

Non-human studies: Several studies have demonstrated that multipotent cells, with the ability to form the ENS when transplanted to uncolonised or aganglionic gut, are present within the gastrointestinal tract during development and into postnatal life [29, 30, 33, 34, 43, 81, 82], including from the ganglionic portion of the gut from an HSCR mouse model (miRet51) [31, 83, 84]. The methodology used to isolate such cells is the culture of dissociated gut to give rise to neurospheres or neurosphere-like bodies (NLBs), akin to stem cell-containing CNS neurospheres. In addition to differentiated neurons and glia, NLBs also contain proliferating undifferentiated cells that not only express putative stem cell markers (e.g. Sox10) but also are capable of self-renewal and giving rise to both enteric neurons and glia. Grafting of postnatal NLBs into aganglionic embryonic mouse gut revealed that donor cells were able to colonise the gut and differentiate into appropriate enteric phenotypes, at the appropriate locations [31].

Recent in vivo studies have shown that ENS stem or progenitor cells have the potential to migrate, proliferate and differentiate into appropriate phenotypes when transplanted into the colon of postnatal mice [35, 43, 85–89]. Such cells can be isolated from the embryonic (E14.5) and postnatal mice gut survived for at least 16 weeks and formed enteric ganglion-like clusters containing neurons and glia. Graft-derived neurons expressed some enteric neuron subtype markers, including NOS, ChAT, calbindin and calretinin. Importantly, intracellular electrophysiological recordings from graft-derived neurons showed that they fired action potentials and received fast excitatory postsynaptic potentials (fEPSPs) demonstrating that the graft-derived neurons had incorporated into the enteric circuitry [43].

Human Studies

A number of groups including ours have reported the harvesting of ENS stem cells from postnatal human gut [36–39, 87, 90–92]. Although initial studies suggested this required full-thickness tissue, our most recent work has shown that gut mucosal biopsies obtained by routine endoscopic procedures can be used as a source of stem cells [39]. Neurospheres were generated in cultures of mucosal tissue from endoscopic biopsies obtained from children from the neonatal period up to 16 years, including HSCR patients (Fig. 49.1). The neurospheres were equivalent to those generated from human embryonic and full-thickness postnatal gut tissue and contained putative ENS stem cells. When transplanted into segments of aganglionic gut, including human HSCR maintained in vitro, the neurosphere-derived cells colonised the recipient gut and generated neuronal phenotypes. These studies highlight a significant advance by identifying a regenerating source of tissue to generate ENS stem cells and confirming the feasibility of autologous transplantation. Although there is data suggesting that transplanted human cells are capable of influencing mouse embryonic gut function [38], it is still unclear if recipient postnatal gut exhibit functional rescue following human ENS stem cell transplantation in vivo [91].

Practical Challenges in Developing Cell Therapies

Although there has been much progress in the sourcing of cells with potential for therapy for gut motility disorders, some key challenges still need to be addressed before effective clinical application. These have recently been discussed in a ‘white paper’ produced by an international consortium of scientific and clinical experts in the field [93].

What Is the Ideal Target Disease?

HSCR has provided the archetypal disease for ENS stem cell therapy. The ENS deficiency (distal intestinal aganglionosis), however, is absolute and extensive, and it is unclear whether replenishment of the complex ENS circuitry is truly achievable. In view of this, perhaps disorders with a less severe anatomical or functional phenotype may be more amenable to therapy.

In oesophageal achalasia, in the early stages of disease, functional and presumably neuronal loss appears more restricted to the lower oesophageal sphincter presenting a smaller therapeutic target. The underlying immunologically mediated pathogenic processes [94], however, may need to be controlled prior to transplantation to prevent destruction of a neo-ENS. In intestinal pseudo-obstruction and slow transit

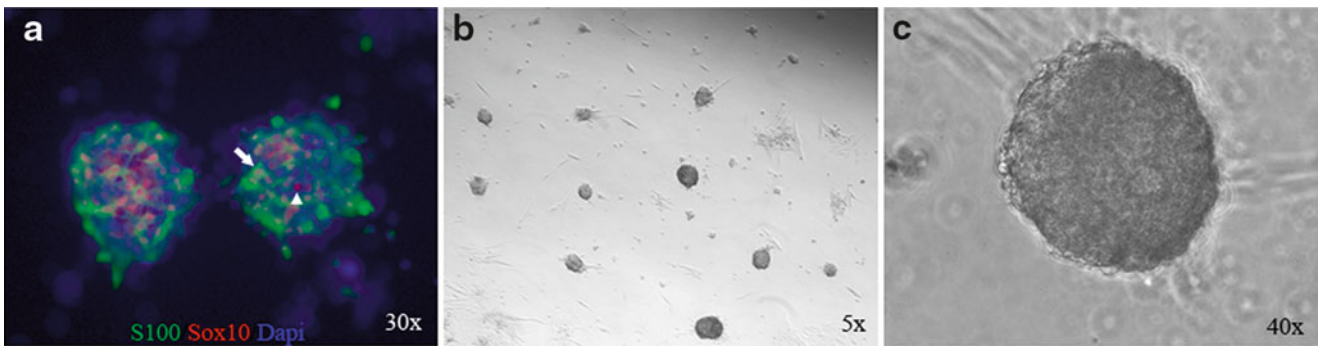

Fig. 49.1 Enteric neural stem cell-containing neurospheres can be harvested from postnatal gut. (**a**) Fluorescent immunostaining of day 14 cell cultures generated from postnatal mouse gut showing the presence of spherical multicellular aggregates of cells, termed neurospheres. These contain cells positive for Sox10 (*red*) and for S100 (*green*). Positivity for both markers (*arrow*) suggests the presence of glial cells, whereas the presence of cells positive for Sox10 only (*arrowheads*) suggests neural crest-derived undifferentiated progenitors or stem cells. (**b** and **c**) Low-power (**b**) and high-power (**c**) bright field images of cell cultures (day 21) generated from dissociated human colonic mucosal biopsies obtained from a 6-year-old patient by conventional endoscopy. The cultures show numerous characteristic neurospheres, which have been shown to contain enteric neural stem cells and can be transplanted into recipient gut

constipation, the overall ENS 'scaffold' appears intact but is clearly dysfunctional possibly due to deficiencies of particular elements of the neuromuscular circuitry [95–97]. These elements, once identified, may be easier to replenish than the entire ENS. Generalised involvement of the long gastrointestinal tract may, however, limit success, as would potential limitations in migration of transplanted cells [98, 99]. It is clear that all these potential disease targets need more detailed characterisation of their specific defects and aetiology prior to the development of any tailored replenishment strategies. Recent international initiatives to address these hold promise [100].

It should be noted that complete ENS restitution may not be necessary. Studies of the ageing gut, where despite substantial neuronal loss, a scanty surviving ENS functions in the absence of any overt functional obstruction, suggest that partial ENS reconstitution may be sufficient to restore some balance between inhibitory and excitatory influences within the neuropathic gut [101, 102]. This suggests that delivery of smaller number of appropriate cells may be an acceptable therapeutic goal.

What Is the Ideal Cell Type?

It is likely that the therapeutic requirement for individual disorders will determine which cell source is most suitable, e.g. whether to use multipotent stem cells (e.g. from hES, iPS) or more committed neuronal precursors (e.g. 'adult stem cells' or precursors sourced from gut). Limitations exist for each source ranging from uncontrolled proliferation and tumour formation (ES cells) to restricted harvesting and differentiation potential (adult stem cells).

The production of unlimited quantities of enteric neurons by direct induction of ES cells remains an exciting possibility, but there remains concern about their potential to form tumours [48, 103] and unwanted cell types. Strategies have been proposed to prevent this including partially differentiating ES cells, enriching for appropriate cell types and then screening for undifferentiated cells [103–105]. Certainly it would be advantageous to differentiate them into specific neuronal subtypes before transplantation. Protocols for such specific differentiation from each stem cell type have yet to be established although some progress has been made. Stem cells from foetal brain (CNS–NSCs) also have the ability to divide, form neurospheres and differentiate into neurons and non-neuronal cells [71, 106]. Micci et al. have reported that CNS–NSCs preferentially differentiate into nNOS neurons [25, 26], which may be promising for conditions such as oesophageal achalasia. For many patients, clinical practitioners and the general public at large, however, there are ethical problems associated with the use of hES cells and CNS–NSCs from fertilised human eggs and aborted foetal brain tissues, respectively.

Much focus has therefore shifted onto 'adult' stem cells, especially given their presumed role in maintaining and repairing the tissue in which they are found and restricted potential to generate only those cell types (e.g. neurons and glia) of the required tissue (e.g. ENS), which limits the need for cell programming and reducing the risk of generating 'ectopic' cell types and malignancy. Such cells, however, are present within much smaller number and appear to have a reduced potential to proliferate. Kruger et al. reported that NC stem cells comprise only <0.2 % of cells within the gut wall of postnatal day 22 rats [34], and human studies have suggested that the generation of ENS stem cell-containing neurospheres declines with increasing postnatal age [39]. Although it is possible to enrich and expand neural stem cells obtained from the ENS [31, 36–39], it is not known whether the therapeutic potential is compromised with prolonged in vitro propagation. The paucity of specific markers for stem cells presents a further potential obstacle for the field. ENS stem cell harvesting has largely been restricted to their isolation within neurospheres, structures composed of a heterogeneous mix of cells consisting of, in addition to the stem cells, differentiated cells including neurons, glia and smooth muscle cells [31, 39]. It may be argued that pure isolation of stem cells is perhaps not necessary as neurospheres exist as potential ready-made stem cell niches and complete therapeutic packages capable of colonising aganglionic gut [31, 37, 39]. However, unless specific isolation is possible, the manipulation of cells within, and generation of targeted cell types from, the heterogeneous cellular pool within neurospheres is likely to be a major problem.

One of the most exciting developments in stem cell science has been the generation of induced pluripotent stem (iPS) cells by the reprogramming of mouse embryonic or adult fibroblasts back to a pluripotent state by introducing four transcriptional factors—Oct4, Sox2, Klf4 and c-Myc [107]. Successful reprogramming of differentiated human somatic cells into a pluripotent state raised the possibility of creating patient-derived stem cells [108], which would bypass both immunological problems and bioethical issues associated with hES cells or those obtained from foetal brains. In terms of the gastrointestinal tract, iPS cells can produce intestinal tissue and gut-like structures in vitro. Three-dimensional intestinal organoids were derived from human iPS cells using activin A treatment to induce endoderm formation, followed by FGF4 and WNT3A manipulations to develop hindgut and intestinal specification [109]. Gut-like structures can also be derived from mouse iPS cells that contain a lumen with three distinct layers (epithelium, connective tissue and muscle layer), neuronal networks and ICCs, and which exhibited spontaneous contractions [110]. It is unknown whether iPS cell-derived gut-like structures or neurons will have any therapeutic relevance for the treatment of enteric neuropathies. Studies will be required to elucidate the mechanisms of reprogramming of somatic cells into

enteric neurons using exogenously delivered transcription factors and to establish a method of purifying desired cells with 100 % frequency in vitro. Interestingly, in recent years, protocols have been developed in vitro whereby both human embryonic stem cells (hESCs) and human pluripotent stem cells (hPSCs) can be converted into neural crest cells (NCC) [111–113]. This was either by the addition of small molecules (SB431542) and Noggin [111] or by activating Wnt signalling (using CHIR99021 (Chir), which works by selectively inhibiting glycogen synthase kinase 3β (GSK-3β) [113, 114] or using the stromal-derived inducing activity of PA6 fibroblast coculture [112]. These culture conditions favour generation of neural crest cells (NCC). The hESC or hPSC-derived NCC could aid in the study of disease pathogenesis, such as defects in cell fate specification, migration and differentiation potential, which in turn could pinpoint area of therapy needed. Most recently seminal work by Fattahi et al. [24] demonstrated that enteric neural crest (ENC) cells can be derived from hPSC. These authors induced neural crest cells from hPSCs followed by treatment with retinoic acid to obtain ENC cells. They showed that hPSC-derived ENC cells gave rise to functioning enteric neurons in vitro and improved survival in *Ednrb*-null mice (mouse model for HSCR) following transplantation. This work provides significant validation for the use of hPSCs for the treatment of enteric neuropathies. However, it remains unclear how transplanted cells were able to elicit the rescue in this study [24]. It also remains to be determined whether transplanting a slightly mixed population of ENS–NCC would be better than a specific pure population as other cell types may provide factors for maintenance and differentiation. Overall, studies such as the above suggest that the ideal cell type for replacement therapies is likely to be a neural crest cell phenotype rather than a generic stem cell population, and deriving them from stem cells may have the advantage of generating adequate cell numbers. However, much work is needed to investigate the function and safety aspects of these transplants.

Is Cell Manipulation Prior to Transplantation Likely to Be Necessary?

The finding that stem cells can be generated from innervated or ganglionic portions of diseased gut or from the thickened nerve trunks characteristic of the aganglionic region of HSCR gut [115] makes it likely that in some cases, especially with autologous transplantation, genetic modification of the cells may be necessary and possible before transplantation. Stem cells derived from the normo-ganglionic or aganglionic part of HSCR gut are likely to have defective biological function, underlining the inability of their predecessors to form a complete or functional ENS [116]. Indeed, enteric progenitors isolated from the monoisoformic Ret51 (miRet51) HSCR mouse model show delayed differentiation compared to controls [83]. These defective cells may have to be rescued by genetic manipulation, given that reintroducing the Ret9 isoform within the miRet51 ENS progenitor cells reverses the differentiation deficits (Natarajan and Pachnis—personal communication). The advent of novel-targeted genome-editing approaches, such as the CRISPR-Cas9 system [117], with their ability to alter genome sequences and gene expression, is likely to provide a significant advance for this aspect of novel stem cell therapy application in humans.

Injection of stem cells in conjunction with missing neurotrophic factors may be beneficial for their survival, migration and differentiation [18]. Recent data suggests this may be possible. Endothelin 3, for example, inhibits reversibly the commitment and differentiation of ENS progenitor cells along the neurogenic and gliogenic lineages, suggesting a role for this factor in the maintenance of multilineage ENS progenitors [118]. Glial cell line-derived neurotrophic factor (GDNF) acting in the presence or absence of endothelin 3 significantly increases the proliferation of ENS progenitors as well as increasing neurite outgrowth [118, 119]. Such findings and studies have enormous implications for pre-transplantation priming of ENS stem cells as well as the creation of receptive environments within recipient aganglionic gut.

Is the Gut Environment Suitable for Cell Replenishment?

In HSCR the average aganglionic segment measures almost 10 cm in length. Yet data from several groups, including ours, suggest that longitudinal migration of transplanted cells within recipient embryonic gut maintained in organ culture may be limited to a few millimetres at best [39]. The limited migratory capacity of grafted stem cells is another potentially important problem, especially in adolescent or older patients, as it appears that the migratory ability of CNS–NSCs and enteric neuronal precursors is limited in more mature gut in which the mesenchyme has already differentiated [25, 98, 99]. It is possible that the local gut environment of patients with congenital gut motility disorders might be defective and/or not be permissive for the grafted cells to survive or differentiate into appropriate cell types. For example, there are reports of decreased expression of GDNF in the aganglionic region of patients even in the absence of mutations in *GDNF* [120]. GDNF has been implicated in the directed migration of NC-derived ENS progenitors within the developing gut during embryogenesis [121, 122]. Therefore, recipient gut may require pretreatment with growth factors, e.g. GDNF, to optimise stem cell transplant success although a recent study using Ednrb-null mice demonstrated that aganglionic gut lacking Ednrb signalling was

permissive to transplanted isogenic enteric neuronal progenitor cells, which were able to engraft and exhibit neuroglial differentiation [89]. More work needs to be done to confirm that the pretreatment of cells, or of the recipient gut of patients, does not have any adverse effects in other aspects of their health.

Finally, immunological rejection of transplanted cells within the gut is also likely to be a problem [123] (Hotta personal communication). This may well be overcome with improving protocols of immunosupression already in use with solid organ and cellular transplantation and by using autologous cells for transplantation.

What Is the Most Effective Route to Deliver Stem Cells to the Gut?

The gut is easier to access compared to the brain or spinal cord, and cells have been introduced into the gut wall of animals through the serosa via laparotomy [25, 27, 28, 44]. Stem cells have also been injected intraperitoneally into animals to replace enteric neurons, but further work is needed to identify all the sites colonised using this method [35, 44]. A recent study has revealed the potential of NC stem cells to give rise to a small number of neurons and glial cells when injected into the peritoneal cavity of *Ednrbsl/sl* rat, but none of the injected cells were found in the aganglionic colon [35]. Injecting cells intravenously could allow cells to be delivered to a broader area which would be an advantage over using multiple injections. However, the vasculature has not yet been explored extensively as a delivery route for cells to the gut.

Endoscopy is routinely practised to deliver drugs into the gut wall. This may be a better way for not only harvesting cells but also for their delivery into recipient guts, as has recently been shown using Ednrb−/− mice [88] especially when combined with imaging techniques for better precision (e.g. ultrasound, confocal). Disadvantages include the need to intubate entire segments of diseased gastrointestinal tract, some of which, e.g. mid-small intestine, remain relatively inaccessible, and would require more complicated enteroscopy techniques.

What Is the Best Measure of the Success of Cell Therapy?

The main aim of cell replacement therapy is to restore function to the diseased gut. Grafted human ENS stem cells have been reported to differentiate into glia and neuronal subtypes reminiscent of a functional ENS within explants of aneural hindgut from chick and mouse embryos [38, 39]. Hotta et al. went on to show that transplanted enteric neural progenitor cells were capable of generating electrically functional enteric neurons in the bowel of postnatal mice [43]. This was a significant step in terms of derivation of functioning neurons from exogenously introduced neuronal progenitor cells in vivo although the authors were unable to address whether transplanted cells integrate into the circuitry of the pre-existing ENS. Very recently, Cooper et al. [42] for the first time achieved functional integration of transplanted cells with host neurons. They isolated enteric neural crest cells (ENCC) from Wnt1-Cre/YFP mice, expanded them in culture and transplanted cells into the colon of wild-type mice. Calcium imaging of transplanted ENCC-derived neurons following stimulation of host enteric nerve fibres demonstrated their functional integrity. However, it remains unclear whether transplanted cell-derived neurons form functional connections to other target cells, including smooth muscle, and/or whether they are capable of forming an ENS with the appropriate circuitry to produce functional recovery on its own accord, particularly when introduced into an aganglionic region. It is likely that functional data will only truly be understood within the context of in vivo studies, by studying parameters ranging from simple gut transit to definitive measurements of peristaltic activity and sphincter function. The study by Cooper et al. also demonstrated the long-term safety of transplanting enteric neural crest cells into the mouse gut. Immunohistochemical analysis and PCR examination of recipient tissues showed long-term survival of transplanted cells without any ectopic spreading or tumour formation at least 2 years following transplantation [42].

Summary and Future Directions

Cell therapy for gastrointestinal motility disorders is an exciting and promising prospect. The ENS has many potential advantages that favour the success of transplantation therapies. These include accessibility to both source and deliver cells, as well as the possibility of minimising immunological rejection by expanding neural stem cells, obtained from unaffected regions of the intestine, for autologous transplantation.

The evidence to date suggests that cells with the potential of generating components of the ENS can be harvested from a range of allogeneic and autologous sources, be propagated and cultured in large numbers and have their biological properties manipulated and ultimately be transplanted into diseased or dysmotile gut to replenish components of the ENS and rescue function. Although a number of significant hurdles remain, all is perhaps not so bleak. Ageing-related neuronal loss is not associated with functional failure giving hope that restitution of a full normal ENS is perhaps not needed. Gene therapy is already established in clinical therapies and rescue of defective ENS stem cells derived from murine models of HSCR possible. Tissue transplantation and management of immunological aspects is well studied and

potentially overcome with the use of autologous transplantation. Recent work has shown that minimally invasive procedures such as endoscopy can be used to isolate ENS stem cells from a regenerating source of intestinal tissue and ultimately to deliver them back into the gut. Transplantation of such cells into models of aganglionic gut suggests they are capable of colonisation, generating components of the ENS and effecting functional change. Although pleasing progress has been seen with enteric neuropathies, other motility disorders such as myopathies and mesenchymopathies will need to see similar initiatives in terms of understanding disease pathogenesis, pathology and ultimately cellular therapies.

There is no doubt that children and adults with gut motility disorders represent a significant challenge in management. Significant strides have been made in teasing away at the processes that underlie the complex workings of the gut neuromusculature, especially the ENS, and have given us tremendous insight into pathogenesis and the identification of putative treatments. Cellular therapies should now be considered alongside these and perhaps herald a shift towards definitive cures for gut motility disorders.

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Chronic Intestinal Pseudo-obstruction Syndrome: Surgical Approach and Intestinal Transplantation

50

Olivier Goulet and Sabine Irtan

Chronic intestinal pseudo-obstruction syndrome (CIPOS) is a severe cause of neonatal or postnatal progressive intestinal failure (IF). This syndrome represents one of the main causes of IF and is characterized by impairment of physical growth and development as well as by a high rate of morbidity and mortality.

The diagnosis of CIPOS is based on typical clinical manifestations, radiological evidence of distended bowel loops with air-fluid levels, and the exclusion of any organic obstruction of the gut lumen [1–5] (see Chaps. 14 and 15). CIPOS is often unrecognized, and the diagnosis, therefore, delayed by several years with useless and potentially dangerous surgeries.

CIPOS can occur in patients with underlying diseases associated with gastrointestinal manifestations (scleroderma, amyloidosis, hypothyroidism, etc.) or be secondary to water-electrolyte disorders (e.g., hypokalemia) and toxic, viral, and parasitic causes. However, in the pediatric age group, most cases are idiopathic and sporadic, even though familial forms with either dominant or recessive autosomal inheritance have been described. Based on histological features, intestinal pseudo-obstruction is classified into three main groups: neuropathies, mesenchymopathies, and myopathies, according to the predominant involvement of enteric neurons, interstitial cells of Cajal, and smooth muscle cells, respectively [6–14] (see Chap. 24). Mitochondrial disorders have been reported [15–17]. Most patients do not show familial recurrence (sporadic cases), but syndromic autosomal dominant [18], autosomal recessive [19], and X-linked [20–23] forms have been described. In particular, an X-linked locus has been mapped to the Xq28 region. Although both familial and sporadic CIPOs have been widely reported, so far only a few genes have been identified as responsible for syndromic CIPO: the thymidine phosphorylase gene (*TP*, also known as endothelial cell growth factor-1, *ECGF1*) [24], the DNA polymerase-γ gene (*POLG*) [25], and *SOX10* [26] (see Chap. 18).

Regardless of the histologic type, CIPOS always involves alterations of smooth muscle contractile function, leading to abnormal intestinal tract peristalsis and nutritional disorders. Manometry can play a supportive role in defining the diagnosis, as well as by showing differences in the manometric pattern of CIPOS [27]. Accompanying uropathies must be sought in patients with CIPOS [28]. The clinical impact of these uropathies may be important and requires specific management by using daily drainage and sometimes, vesicostomy.

Longitudinal surveys have been published [29–35], including a large multicenter French pediatric study [31]. Long-term outcomes are generally poor despite surgical and medical therapies and characterized by disabling and potentially life-threatening complications. Treatment of CIPOS involves nutritional, pharmacological, and surgical therapies, but is often frustrating and does not change the natural course in the majority of cases [36–39]. The nutritional management has a crucial importance in pediatric age and involves enteral delivery of special formulae, by nasogastric tube, percutaneous gastrostomy, or jejunostomy [36, 37]. In the most severe cases, parenteral nutrition becomes mandatory in order to satisfy nutritional requirements and appropriately manage obstructive episodes [36].

Surgery is one of the mainstays of CIPOS therapeutic management. Surgery is performed in a variety of situations in pediatric patients, but surgical options must be evaluated carefully. There is no consensus regarding indications and procedures. This chapter aims to review the main situations in which surgery may be required.

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Surgery for Diagnosis

Variable clinical presentation and lack of other specific diagnostic tests often lead to surgery being required for diagnosis. Nevertheless, unnecessary laparotomy could be avoided

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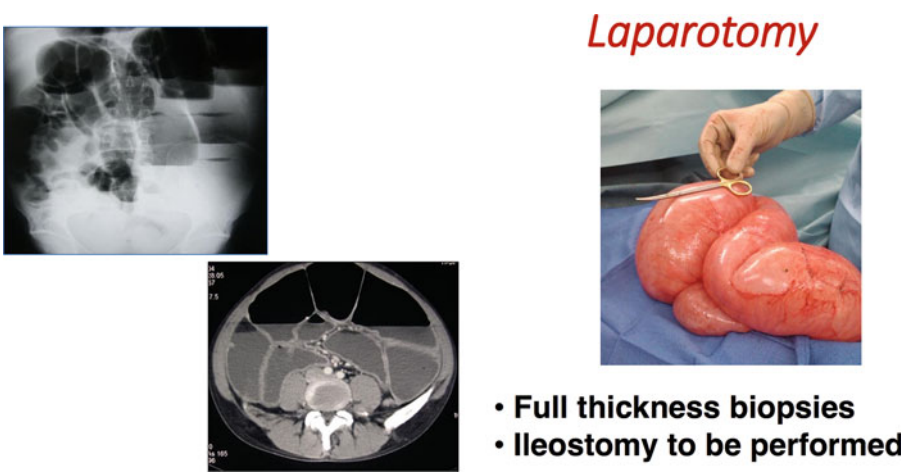

Fig. 50.1 Laparotomy for chronic intestinal pseudo-obstruction

since diagnosis is mostly based on clinical and radiological symptoms of intestinal obstruction. It is not unusual, however, for some patients, especially children and adolescents with an acute presentation, to undergo an exploratory laparotomy (Fig. 50.1). In the absence of organic obstruction observed at this laparotomy, we suggest that a medico-surgical discussion be undertaken to consider:

- Performing intestinal full-thickness biopsies at different levels for histopathologic analysis
- Performing an enterostomy according to the level of intestinal distension

In reality, in most cases, the acute presentation and subsequent surgical procedure do not occur at a specialized center, and these suggested interventions are not done. Such issues are controversial, but we do propose that if the diagnosis of CIPOS is strongly suggested from the surgical exploration, careful biopsies should be performed. Regarding enterostomy, our experience tends to suggest that if it is not performed at first laparotomy, it will need to be done later but with subsequent increased risk of peritoneal adhesions.

In summary, patients with evidence of CIPOS from clinical and radiological presentation should not be operated on to make the diagnosis. Patients who undergo laparotomy for enterostomy because of permanent or recurrent intestinal obstruction should have intestinal full-thickness biopsies for specific diagnosis. This should be done regardless of the patient's age. Appropriate tissue sampling, handling, and expert interpretation are crucial to maximize diagnostic accuracy and reduce interobserver variability. The absence of validated age-related normal values for neuronal density, along with the lack of correlation between clinical and histological findings, results in significant diagnostic uncertainties while diagnosing quantitative aberrations such as hypoganglionosis or ultrashort Hirschsprung disease. Intestinal neuronal dysplasia remains a histological description of unclear significance [40].

Surgical Procedures for CIPOS

Gastroparesis

Gastroparesis is a frequent expression of CIPOS. Bowel decompression by a gastrostomy is often required. Repeated acute episodes of bowel obstruction and chronic intestinal distension require bowel decompression by using nasogastric suction. The placement of a venting gastrostomy is of great benefit in avoiding the recurrent placement of nasogastric tubes. When surgery is required, a gastrostomy may be performed during the same surgical procedure. If a gastrostomy is not surgically placed, percutaneous endoscopic gastrostomy tube (GT) placement is easily achieved in these children. Since enteral feeding should always be preferred to using parenteral nutrition (PN), intragastric administration of feeding may be achieved by the GT as continuous or bolus enteral tube feeding. Gastric decompression by repeated and even permanent gastric drainage is not always sufficient. Surgical procedure such as pylorotomy or gastroenterostomy may be discussed with caution according to the risk of overloading a poorly motile intestine without any clear functional benefit and clinical improvement.

Enterostomy

In neonates and young infants, intestinal obstruction may last several weeks requiring total parenteral nutrition (TPN) with subsequent complications including catheter-related sepsis and liver disease [4]. Enterostomy may offer the chance to restart intestinal transit allowing feeding and reducing the need for PN.

In some patients, attacks of intestinal obstruction are frequent and/or life threatening. Chronic bowel dilatation impairs intestinal motility creating a vicious circle which increases intraluminal bacterial overgrowth with the subsequent risk of

intestinal translocation, enterotoxin release, and liver disease [41, 42]. Enterostomy should be performed to bypass the functional obstruction and obtain digestive decompression.

The location of the enterostomy is a matter of debate. In cases of obvious megacystis microcolon syndrome, a terminal ileostomy is certainly required. Otherwise, we do recommend performing a terminal ileostomy and avoiding a colostomy whatever the clinical presentation or histopathologic pattern. It is important to consider the so-called ileocecal brake as the segment that should be short-circuited. In our experience, all patients who first underwent a colostomy went on to have formation of a terminal ileostomy or jejunostomy. In some case, a venting ileostomy using the Santulli or Bishop-Koop procedure may be attempted with the aim of maintaining colonic function and avoiding diversion colitis (DC) (see below).

The outcome after ileostomy or jejunostomy varies according to the location of the enterostomy and to the disease itself. The literature does not provide any evidence of a histopathology-related prognosis even if the survey reported by Henyeke et al. suggested worse prognosis of myopathies and that they all need ileostomies [32]. However, much fewer than 50 % of patients improve after ileostomy by being weaned from PN. In our opinion, enterostomy, as distal as possible, is the most logical approach. Terminal ileostomy usually enables transit to resume and leads to a major long-term reduction in obstructive episodes. We currently perform an ileostomy to obtain durable intestinal autonomy and PN weaning, with the future plan to do a total or subtotal colectomy with ileorectal or ileosigmoid pull-through [33].

A paper by Irtan et al. reported stomal prolapse in children with chronic intestinal pseudo-obstruction as a frequent complication [43]. Twenty-two out of 34 (65 %) CIPOS children referred to their center between 1988 and 2008 had a stoma and were compared with 22 other children referred for another pathology necessitating a stoma. The incidence of stomal prolapse in CIPOS children was 45 % vs. 9 % in non-CIPOS children ($p = 0.01$). Prolapse occurred between the first postoperative day and the tenth postoperative month, with a median of 2 months. Surgical management was required in 60 %, with an intestinal necrosis rate of 20 % leading to intestinal resection. The authors did not identify particular risk factors favoring stomal prolapse.

Percutaneous endoscopic cecostomy or colostomy (PEC) is increasingly proposed as an alternative to surgery to treat CIPOS and relapsing sigmoid volvulus [44–47]. Cecostomies or even sigmoidostomies have been used to administer antegrade enemas when intractable constipation appears to be the prominent symptom. A few reports are available both in children and adults describing the indications, complications, and outcomes. A retrospective, single-center study involving eight adults was reported by Lynch et al. [46]. Six patients had CIPOS and two had chronic constipation. The use in seven of eight cases resulted in clinical improvement with reduction of intestinal obstruction episodes and improved feed tolerance. One patient suffering chronic constipation required surgical removal of the percutaneous endoscopic cecostomy tube at 4 days for fecal spillage resulting in peritonitis despite successful tube placement. Removal of the cecostomy tube occurred in three of six cases of pseudo-obstruction (the other three remain in place). In the other patient with chronic constipation, clinical improvement occurred, but the patient died of underlying illness 21 days after placement. A case of acute stercoral peritonitis was reported [47]. At laparotomy, the colostomy flange was embedded in the abdominal wall, but no pressure necrosis was found at the level of the colonic wall. This complication was likely related to inadvertent traction of the colostomy tube. Percutaneous endoscopic cecostomy is considered by some authors as a viable alternative to surgically or fluoroscopically placed cecostomy in a select group of patients with recurrent colonic pseudo-obstruction or chronic intractable constipation.

Closure of the Stoma

In children whom a decompression ileostomy has produced relief, but there is diffuse disease, the urge to reestablish connection with the defunctioned limb of the bowel should be resisted as this will only result in further episodes of obstruction. In other words, performing an ileostomy and closing it because of clinical improvement results in the patient undergoing two surgical procedures without resolution of the primary issues. This should be avoided. Conversely, in patients in which clear improvement from ileostomy is observed, with PN weaning and at least 2 years follow-up on enteral tube feeding or oral feeding without exacerbations, total colectomy and ileorectal anastomosis with the Duhamel procedure may be considered. In our experience, two thirds of the patients who underwent this procedure remain off PN for a long period of time [33].

Recurrent Laparotomies and Enterectomy

In the past, many patients underwent multiple surgical procedures. Unnecessary abdominal surgery in children with CIPOS should be avoided because they bear the risk of prolonged postoperative ileus and developing adhesions, creating a diagnostic problem each time there is a new obstructive episode. Mechanical obstruction should be considered in patients with an enterostomy who continue to present with exacerbations of bowel obstruction. In an earlier study involving only seven patients, surgery was performed as a treatment 21 times with a mean of three procedures per patient [30].

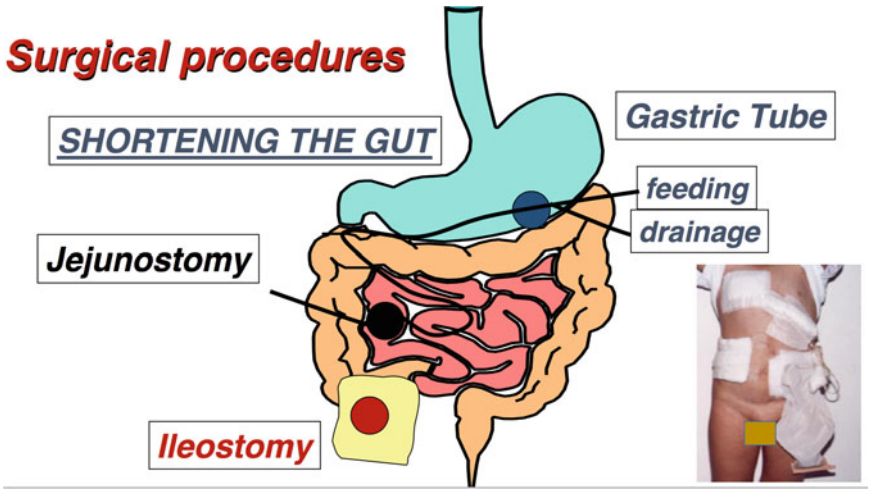

Fig. 50.2 Surgical procedures for chronic intestinal pseudo-obstruction

This is similar to other data reported. In one study, 67 surgical procedures were performed in 22 patients [8], and in another study involving 105 pediatric infants and children, 71 patients underwent surgery during their illness, with 217 surgical procedures [31]. An ostomy was the most performed procedure. Surgery may cause adhesions, so interpretations of postoperative obstructive episodes are difficult. Exploratory laparotomy for obstruction should be performed only when a clear mechanical obstruction has been demonstrated which remains very difficult to assess. Signs of peritonitis, extreme dilatation, and pain in association with specific episodes of obstruction point more toward mechanical rather than functional obstruction, and a laparotomy may be required to relieve it.

Patients with CIPOS or chronic intractable constipation (CIC) may develop anatomical obstruction such as colonic volvulus, with presenting symptoms mimicking those of underlying pseudo-obstruction. Patient records of eight children with colonic volvulus were retrospectively reviewed [48]. The mean age at presentation with colonic volvulus was 13.2 ± 5.05 years. All patients presented with worsening of abdominal distension and pain. The mean duration of symptoms of colonic volvulus before seeking medical help was 4.2 days (range 1–7 days). Water-soluble contrast enema was the single most useful investigation for confirming the diagnosis. All patients required surgery. There was no mortality associated with colonic volvulus. Clinicians should be vigilant and include volvulus in the differential diagnosis of the acute onset of abdominal distension and pain in patients with CIPOS and CIC. Delay in diagnosis can result in bowel ischemia and perforation.

Some patients, in whom there is segmental bowel dilatation but no evidence of mechanical obstruction, have been reported to benefit from segmental resections or to have improved following placement of a jejunostomy tube within the dilated loop [49, 50]. In our experience, the use of this jejunostomy button device for daily intermittent bowel decompression can effectively improve bowel function allowing decreased PN intake. However, one should consider the quality of life (QOL) of a child with three tubes and, for most of the time, a central line (Fig. 50.2).

Patients suffering from CIPOS clearly benefit from home parenteral nutrition (HPN) to maintain adequate nutritional status and general health [51]. However, permanent and severe intestinal dysmotility can seriously disturb the QOL to the point of making it intolerable [52, 53]. Subtotal enterectomy [54, 55] and bilateral thoracoscopic splanchnicectomy have been proposed in severe CIPOS [56]. A retrospective study of eight patients with end-stage CIPOS maintained on HPN and suffering from chronic occlusive symptoms refractory to medical treatment underwent extensive small bowel resection preserving less than 70 cm of total small bowel and less than 20 cm of ileum [55]. The jejunum was anastomosed either to the ileum or to the colon. Six patients were completely relieved from obstructive symptoms. Two patients needed a second operation to remove the residual ileum because of recurrent symptoms. Both were significantly improved and there was no postoperative death. All patients experienced a significant improvement in their QOL. Near-total small bowel resection appears to be a safe and effective procedure in end-stage CIPOS patients, refractory to optimal medical treatment.

The implantation of gastric or intestinal pacemakers aimed at improving motility constitutes a promising investigational approach in patients with severe motility disorders. The use of gastric electrical stimulation has been shown to significantly improve nausea and vomiting not only in patients with diabetic gastroparesis but more recently also in three adult patients with familial and one with postsurgical CIPOS with disabling nausea and vomiting [57]. The weekly vomiting frequency decreased from 24 before implantation of the gastric pacemaker to 6.9 after 12 months. The clinical response was unrelated to the presence of, or improvement in, delayed gastric emptying in these patients. Although placements of the electrotrodes along the

anterolateral surface of the stomach was successful in most patients by laparoscopic implantation, the procedure was not without risk since the electrodes caused ileus necessitating explantation and short intestinal resection [57, 58].

Diversion Colitis

Diversion colitis (DC) is the inflammation of the excluded segment of the colon in patients undergoing ostomy. Long-lasting terminal ileostomy for CIPOS may result in DC [59]. We already experienced this rare complication requiring, most of the time, a total colectomy. DC may be an indolent inflammatory nidus and a potential cause for repeated bacteremia, abdominal pain, and bleeding. DC has been reported in 11 of 14 children, 4 months to 7 years after surgical diversion of the colon for CIPOS [60]. The children had complained of diffuse, poorly localized abdominal pain and a history of bloody stools in three children. Both colonoscopy and biopsies showed a nonspecific acute and chronic inflammation and/or nodular lymphoid hyperplasia. Authors failed to show any correlation between the duration of the colonic diversion and the severity of the colitis. Usual histology of the bypassed segment is characterized by diffuse follicular lymphoid hyperplasia; lamina propria expansion by plasma cells, lymphocytes, and some neutrophils; cryptitis; reactive epithelium; and mucin depletion. Crypt abscesses, aphthous ulcers, mild architectural distortion, and Paneth cell metaplasia may be noted in the most severe cases [61]. DC may be an inevitable consequence of colonocyte nutrient deficiency and may be superimposed by a second insult, such as a low-grade pathogen. Treatment modalities usually include surveillance for paucisymptomatic patients, restoration of bowel continuity for severely symptomatic cases, and the use of short-chain fatty acid (SCFA) enemas in selected cases. It is suggested that a change in colonic microbiota may lead to colitis; however, direct evidence for this disease progression is poorly established. A study involved 48 patients: 26 DC patients and 22 in the control group [62]. Differences were observed between the two groups in the levels of *Staphylococcus* ($p = 0.038$), *Enterococcus* ($p < 0.001$), *Klebsiella* ($p < 0.001$), *Pseudomonas* ($p = 0.015$), *Lactobacillus* ($p = 0.038$), the presence of anaerobes ($p = 0.019$), and *Bifidobacterium* ($p < 0.001$). A significant correlation between the severity of colitis and bacterial composition was only observed for *Bifidobacterium* ($p = 0.005$, correlation coefficient $= -0.531$). In case of CIPOS, according to the risk of infection, and the need of permanent ostomy, total colectomy is, in general, required. Otherwise, Santulli or Bishop-Koop procedure may be attempted with the aim of restoring partial colonic function and resuming DC.

Intestinal Transplantation

Intestinal transplantation (ITx) has become a lifesaving procedure for patients with irreversible intestinal failure (IF) [63–65]. Indications for ITx include not only extreme short bowel syndromes but also all situations in which the small intestine is unable to achieve nutritional requirements; these include inborn errors of intestinal mucosa development (intestinal epithelial dysplasia, microvillus inclusion disease) or severe motility disorders such as CIPOS [63]. Approved indications for ITx include liver dysfunction, loss of major venous access, frequent central line-related sepsis, and recurrent episodes of severe dehydration despite intravenous fluid management. Surgical options include transplantation of the isolated intestine, combined liver-intestine transplantation, or multivisceral transplantation of the stomach, duodenum, pancreas, and small bowel (with or without the liver). Immunosuppression for ITx is based on tacrolimus therapy, often with induction immunosuppression using antilymphocyte antibodies (e.g., antithymocyte antibody and alemtuzumab). The intestinal transplant registry reported recently 82 programs that reported 2887 transplants in 2699 patients [66]. Regional practices and outcomes are now similar worldwide. Current actuarial patient survival rates are 76 %, 56 %, and 43 % at 1, 5, and 10 years, respectively. Rates of graft loss beyond 1 year have not improved. Grafts that included a colon segment had better function.

In many cases of CIPOS, outcome is poor, with a constant risk of sepsis from intestinal bacterial overgrowth and water-electrolytic disorders related to intraluminal fluid retention. In addition, patients almost permanently dependent on gastric drainage have a poor quality of life and are thus candidates [52, 53]. Indeed, ITx is the only definitive curative treatment especially when many medical and surgical attempts failed. ITx with or without liver transplantation is required in patients with primary neuromuscular disease and PN-related complications such as progressive or end-stage liver disease or for those whose intravenous access has become unreliable and precarious because of repeated sepsis and extensive thrombosis. Transplant procedures vary according to indication for liver transplant and based on the experience of the transplant surgical team [48–50] (Fig. 50.3). Combined small bowel-liver transplantations or multivisceral transplantations including the stomach have been performed in refractory forms of CIPOS associated with end-stage liver disease [67–70]. Multivisceral transplantation (MVTx) was reported in 16 children with a median age of 4 years [68]. Indications for MVTx were liver failure ($n = 10$), loss of venous access ($n = 3$), or sepsis ($n = 3$). Modified MVTx without the liver was performed in six patients. Reported actuarial patient survival for 1 year/2 years for period was 57.1 %/42.9 % and 88.9 %/77.8 %.

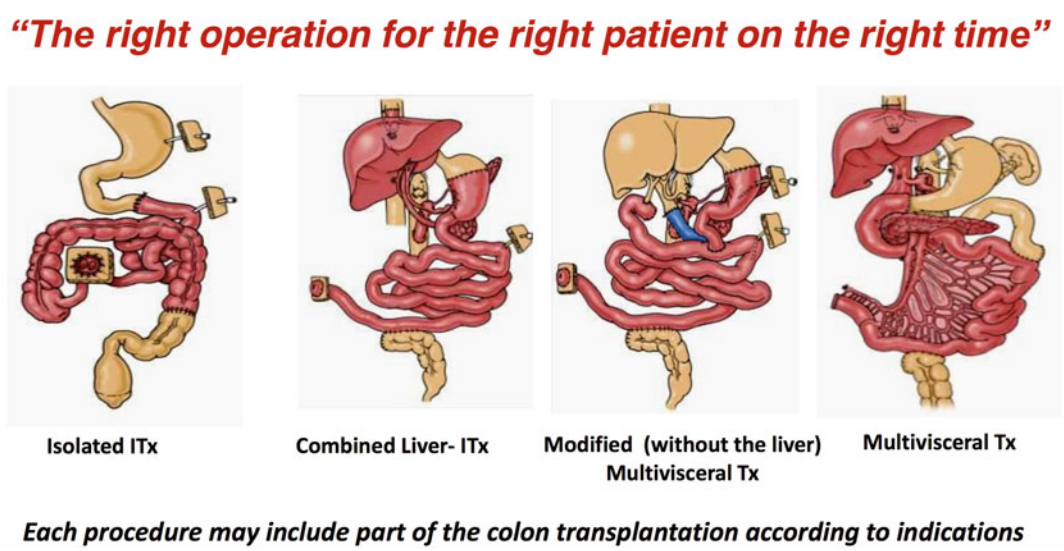

Fig. 50.3 Intestinal transplantation surgical techniques

None of the long-term survivors remained on PN and all tolerated enteral feeding. Gastric emptying was substantially affected in one case. Bladder function did not improve in those with urinary retention problems. MVTx for CIPOS offers a lifesaving option with excellent function of the transplanted pancreas and stomach among survivors.

ITx may represent the only definitive cure for patients with permanent IF due to CIPOS. However, graft rejection and immunosuppression-related lymphoproliferative disorders are more common than after other organ transplants. It is not yet established if the results of ITx achieved in CIPOS patients are equivalent to those experienced with other causes of IF such as short gut syndrome, total aganglionosis, microvillous inclusion disease, or epithelial dysplasia [66]. Complications seem to be more common due to multiple previous abdominal surgeries, dysmotility of the stomach and esophagus, and extraintestinal manifestations including associated anomalies of the urological, immune, and neurological systems. An extensive workup including a search for mitochondrial disorders should be performed before any discussion of ITx, and careful consideration is required before transplantation is undertaken. Determining the extent of the disease process (which may involve any part of the gastrointestinal tract) and the type of organ transplantation required is mandatory. Early referral is essential on initial presentation of these patients to enable optimal medical care and ensure that transplantation remains an option [44, 53].

Ethical dilemna may arise with children who will never be able to tolerate full enteral feeding. Some patients with severe CIPOS may be disabled because of chronic, massive GI dilatation refractory to stomal decompression or partial enterectomy. The poor quality of life might serve as indication for ITx, and not the usual criteria, which include progressive liver disease, loss of vascular access, and repeated life-threatening sepsis. In any case, parents must be extensively informed about the risks of the procedure and about the outcomes of all decisions.

Conclusion

Primary CIPOS is a rare condition with a variable clinical expression. Medical management remains difficult and prognosis poor. Histological studies are essential to classify the syndrome, even if manometric data are able to differentiate between myopathic and neuropathic forms and although histological type does not appear to influence management and long-term outcome. A trained multidisciplinary team, including surgeons, gastroenterologists, and a home PN coordinator, should assume the management of these patients which may involve a PN program and transplant surgery [71, 72]. For many reasons (nutrition, prevention of infectious complications, etc.), an enterostomy (preferably an ileostomy) is often performed as one of the first therapeutic measures. The "permanent" surgical reconstruction, designed to be minimally obstructive, is only envisaged after a long period of stability and if possible when the child is weaned from long-term PN. Intestinal transplantation may be the last therapeutic option when all medical and surgical approaches have failed. The management of CIPOS pediatric patients requires the cooperation of a group of specialists: the disease has to be confirmed by a number of tests to avoid mistakes in the differential diagnosis. The treatment should be aimed at relieving symptoms arising from gut dysmotility (ideally using prokinetic agents), controlling abdominal pain (possibly with non-opioid antinociceptive drugs), and optimizing

nutritional support. Furthermore, a thorough diagnostic workup is mandatory to avoid unnecessary (potentially harmful) surgery and to select patients with clear indication to intestinal or multivisceral transplantation.

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